PROTOCOL
for

MEDICAL THERAPY OF PROSTATIC SYMPTOMS

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Distributed by the

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Third Edition: July 25, 1996
Updated: January 10, 1997
Updated: March 10, 1997
Updated: July 3, 1997
Updated: October 10, 1997
Updated: February 25, 1998
Updated: October 13, 2000

PREFACE

Editions of the Protocol

The protocol for Medical Therapy of Prostatic symptoms (MTOPS), sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK-NIH), describes the background, design, and organization of the trial. The protocol will be maintained by the Biostatistical Coordinating Center (BCC), which is The George Washington University Biostatistics Center, over the course of the trial through new releases of the entire protocol or issuance of supplemental protocol memoranda. Comments or questions regarding aspects of this protocol, including distribution, should be directed to the staff of the BCC at the address shown on the front cover.

First Edition

The first edition of the protocol (dated, June 5, 1995) was based on the pilot study protocol jointly written by members of the pilot study Steering Committee and modified during the transition to the full-scale trial by members of the full-scale Steering Committee.

Second Edition

The release of the second edition of the protocol (dated, October 23, 1995) followed modifications to the protocol, by the members of the Steering Committee, prior to initiation of participant recruitment. The second edition includes the following major changes to the first edition:

1) Monitoring Baseline Prostate Volumes

Rationale: Of the 140 prostate volumes determined during the baseline period of the pilot study, a total of 30 randomized participants had total gland prostate volumes < 20 cc (21%) and an equal number had volumes > 50 cc. The Steering Committee decided to limit the number of prostates < 20 cc in order to minimize the number of randomized participants without defined BPH and to ensure the placebo group's clinical progression of BPH rate used in the sample size determination. They also decided to ensure an appropriate number of prostate volumes > 50 cc for a subgroup analysis of secondary outcomes by randomizing baseline prostate volumes > 50 cc in a proportion similar to the pilot study.

Text of Amendment:

a) Added after line 25 on page 6:
"5. Prostate volume"

b) Added after line 11 on page 13:
"6. Transrectal ultrasound (TRUS)."

c) Eliminated item "6" on line 26 of page 12 and renumbered.

d) Informed consent document in Appendix A:
i) Inserted between the 5th and 6th paragraph of the "PROCEDURES":
"If the above tests indicated that you are eligible, a second visit will be scheduled. At the second visit your vital signs, uroflowmetry and PVR will be measured again. You will complete two questionnaires that determine the severity of your urinary symptoms and your general health. The size of your prostate will be measured by transrectal ultrasonography. This ultrasound is done by placing a small probe into your rectum. This procedure may cause slight discomfort resulting from the placement of the ultrasound probe into the rectum."
ii) Added to the end of the 1st paragraph of the "RISKS":
"This includes slight discomfort with placement of the ultrasound probe during the prostate ultrasound".

e) Modified the table in Appendix G:
i) Added a row for "TRUS" following the row for "Flow Rates" and placed an "X" in the "Screen 2" column only
ii) In the TRUS and Biopsy Substudy section, eliminated the "X" under the "Screen 2" column in the "TRUS" row.

f) Added paragraph E to Section 5, Randomization of Participants:
"E. Modifying Recruitment Based on Monitoring Prostate Volumes"

2) Additional Testing at the Time of the Primary Outcome

Rationale: For participants enrolled in the transrectal ultrasound (TRUS) and biopsy of the prostate substudy, a TRUS and needle biopsy of the prostate is conducted and a serum sample for hormone analysis is collected at screening visit #2, at 12 months post-randomization and at last follow-up visit. The Steering Committee decided that it is important to collect this information at the time of confirmed clinical progression of BPH (i.e., the primary outcome) to document changes at the time of the primary outcome.

Text of Amendment:

a) Changed (noted in italics) lines 15-20 on page 16:
Serum samples will be taken at 6 months (for PSA only), at 12 months, yearly thereafter, *and at the last visit* for PSA, chemistry, and hematology analysis (see

Appendix E for details of hematology and chemistry analyses). A physical exam and urinalysis (see Appendix E) will be performed yearly *and at the last visit*. The sexual function (see Appendix C) and MOS-36 Health Survey (see Appendix D) questionnaires will be administered yearly *and at the last visit*.

b) Added the following paragraph after line 29 on page 16:
"For participants of the ultrasound and biopsy of the prostate substudy, the following procedures are performed at 12 months post-randomization, at the time of the primary outcome (i.e., clinical progression of BPH) and the last follow-up visit: transrectal ultrasound and needle biopsy of the prostate and collection of a serum sample for analysis of hormones."

c) Modified the table in Appendix G:
In the TRUS and Biopsy Substudy section, change the superscript of "1" in the "Time (Months) = 72" column to "2" and add the following footnote: "2: at the time of the primary outcome (clinical progression of BPH) and last visit"

3) Miscellaneous

The following clarifications and corrections were made during the release of the second edition of the protocol.

a) Added to the end of line 11 on page 5:
"...confirmed within 4 weeks."

b) Added to the end of line 16 on page 5:
"...confirmed 2 to 4 weeks later."

c) Added to the end of lines 15 and 22 on page 6:
"...and impact index"

d) Modified (noted in italics) lines 10-13 on page 18:
"Reporting of adverse events will be accomplished by collecting information on adverse experiences at each follow-up visit. *Occurrence of an adverse event will be indicated on the standard follow-up visit case report form and detailed on the adverse event report form.*"

e) Modified (noted in italics) lines 14-16 on page 18:
"In order to facilitate timely reporting of certain serious adverse events, *the Adverse Event Report* will be filled out immediately and directed to the BCC, where the BCC medical consultant will serve as the *serious adverse event report* monitor."

f) Added to the end of line 16 on page 20:
"...except for titration visits)"

g) Added after line 20 on page 20:
"5. Titration Visit Inventory: Vital Signs, Compliance, Adverse Events (administered at end-weeks 3 and 4 of any titration period)"

h) Modified (noted in italics) line 10 on page 29:
"...Chair *and Vice-Chair* of the Steering Committee"

i) Modified (noted in italics) lines 11-14 on page 30:

Transition Phase	01APR1995 to 30*NOV*1995	(*8* months)
Randomization Phase	01*DEC*1995 to 30*NOV*1997	(2 years)
Follow-up Phase	01*DEC*1995 to 30*NOV*2001	(6 years)
Close-out/Analysis Phase	01*DEC2001* to 31MAR2002	(*4* months)

j) Modified the table in Appendix G:
In the All Participants section, added "and PVR" to the row labeled "Flow Rates"

Second Edition (Updated 03/25/96)

An update (dated, March 25, 1996) to the second edition of the protocol followed modifications to the protocol made during the Steering Committee meeting held on March 6, 1996. The update includes the following major changes to the second edition:

The Steering Committee decided to eliminate the PSA collection at the 6 month follow-up visit.

Text of Amendment:

a) Changed lines 15-17 on page 16:
“Serum samples will be taken at 12 months, yearly thereafter, and at the last visit for PSA, chemistry, and hematology analysis (see Appendix E for details of hematology and chemistry analyses).”

b) Changed lines 29-30 on page 18:
“Serum prostate specific antigen (PSA) assays will be performed by the Diagnostic Center at baseline, 12 months and yearly thereafter.”

Third Edition

The release of the third edition of the protocol (dated, July 25, 1996) followed modifications to the protocol made by the Principal Investigators by ballot since the

Steering Committee meeting on March 6, 1996 and at the last Steering Committee meeting on July 12, 1996. The update includes the following major changes to the second edition:

1) Change of study name

The Steering Committee voted to name the study "Medical Therapy of Prostatic Symptoms (MTOPS). Changes were made in all relevant places.

2) Inclusion of patients using topical anti-cholinergic medications for glaucoma

The Principal Investigators voted to include patients who are using anti-cholinergic eye drops for glaucoma.

Text of Amendment:

a) Added lines 5-7 on page 9:
"...with the exception of topical anti-cholinergic eye drops used for glaucoma for more than 3 months prior to the first screening visit."

3) Inclusion of patients taking cimetidine

The Principal Investigators voted to include patients who have taken cimetidine, an H_2 blocker with anti-androgen effects, to be randomized following a 3 month washout period.

Text of Amendment:

a) Added to lines 11-12 on page 9:
“If the patient has taken prescription cimetidine within 3 months prior to the first screening visit.”

4) Change of waiting period between cystoscopy or biopsy and screening

The Principal Investigators voted to change the exclusion criterion of patients who have cystoscopy or biopsy within the past two weeks to the past one month.

Text of Amendment:

a) Modified (noted in italics) lines 29-30 on page 9:
“Active urinary tract disease or has undergone cystoscopy or biopsy of the prostate within *one month* prior to the first screening visit ...”

5) Additional information to clarify unmasking procedure

Text of Amendment:

a) Added lines 17-23 on page 11:
"If, however, there is a serious adverse event which is thought by the clinical center staff to be possibly or probably related to the coded medication, the clinical center staff, when necessary for the safety of the participant, will unmask treatment group assignment upon conferring with the clinical center's principal investigator. In this event, the clinical center staff must promptly contact the BCC with an explanation of the need for unmasking the treatment group assignment. A detailed written report must also be submitted to the BCC within three working days of the initial BCC contact."

6) Added the statement of the collection of confidential information to the Prototype Informed Consent

Text of Amendment:

a) Informed Consent Document Prototype in Appendix A, inserted at the end of the 2nd paragraph of "PROCEDURES":

"To maintain contact with you, personal identification information will be recorded. This confidential information will only be available to the staff of the (...name of institution conducting study...) connected with this study."

7) Miscellaneous

a) Modified (noted in italics) lines 31-32 on page 15:
"Doxazosin (or its placebo) will be *shipped in bulk by the pharmaceutical manufacturer to the drug distribution center for packaging, labeling and distribution*..."

b) Clarified (noted in italics) lines 22-23 on page 16:
"If the participant does not continue in the study, *a major follow-up visit will be conducted at the last patient visit*."

c) Modified (noted in italics) line 36 on page 18 through line 4 on page 18:
"The correction algorithm will be: (1) for participants on placebo or doxazosin only, the PSA value will be multiplied by one and (2) for participants on finasteride only or finasteride plus doxazosin, the PSA value will be multiplied by two *plus a correction factor for odd-numbered values.*"

d) Modified Appendix G: Follow-up Schedule for Full Scale Trial: Removed the indicator for Six Month PSA.

e) Added a list of abbreviations used in the Protocol following the Table of Contents.

Third Edition (Updated 01/10/97)

This update (dated, January 10, 1997) to the third edition of the protocol followed modifications to the protocol made during the Steering Committee meeting held on November 8, 1996. The update includes the following major changes to the third edition:

1) Additional patients will be included in the biopsy substudy

Changes were made to incorporate the additional number of patients that will be included in the biopsy substudy due to new funding.

Text of Amendments:

a) Changed (noted in italics) line 29 on page 6 through line 2 on page 6: "A key feature of this protocol is the inclusion of predetermined tissue biopsies that will be obtained to evaluate the status of the prostate before and after medication in *approximately half of the* randomized participants."

b) Changed (noted in italics) line 24 on page 7: "*Approximately half* of the randomized participants will undergo TRUS and biopsy of the prostate with the collection of a serum sample for analysis of hormones."

2) Urodynamics Substudy

The addition of the Urodynamics Substudy was incorporated in all relevant places.

Text of Amendments:

a) Added a description of the substudy after page 7.

b) Added the urodynamics procedure to the description of the screening period on lines 20-21 on page 13: "For participants of the urodynamics substudy, the urodynamics procedure will also be performed during SV2."

c) Added the urodynamics procedure to the follow-up protocol on lines 35-36 on page 17:
"For participants of the urodynamics substudy, the urodynamics procedure is performed at the last follow-up visit."

d) Added the Urodynamics Subcommittee to the list of subcommittees on lines 25-28 on page 29:
"...and Urodynamics Subcommittee."

e) Modified the table in Appendix G: Follow-up Schedule for Full-Scale Trial as follows:

Added a Urodynamics Substudy Section following the section for TRUS and Biopsy Substudy which includes a row for the Urodynamics procedure and placed an "X" in the "Screen 2" column and an "X[1]" in the "72 Week" column indicating at 72 weeks or last visit.

3) Clarified exclusion criteria regarding any evidence of bladder or prostate cancer

Text of Amendment:
a) Added (noted in italics) a clarification to exclusion #20, lines 7-11 on page 10:
"20. Cancer which is not considered cured (except basal cell or squamous cell carcinoma of the skin). A potential participant is considered cured if there has been no evidence of cancer within five years of randomization. *Evidence of bladder cancer or prostate cancer is exclusionary whether the patient is considered cured or not.*"

4) Addition of New Case Report Forms

Three new case report forms were added: Urodynamics Information (P02), Non-scheduled Biopsy Information (P04) and Recruitment Source Tracking Information (T02).

Text of Amendment:

a) Added Form T02 to the list of baseline forms, line 12 on page 20:
"5. Recruitment Source Tracking Information"

b) Added Forms P04 and P02 to the list of other specific forms on page 21:
"6. Urodynamics Information"
"7. Non-scheduled Biopsy Information"
"14. Clinic Review Committee Report"

c) Added tracking forms to the list of eligibility procedures, line 1 on page 13:
"8. Tracking information (patient information and recruitment source)."

5) Miscellaneous

Text of Amendment:

a) Changed (noted in italics) lines 6-8 on page 18:
"Decisions *based on the PSA value* concerning the need for additional prostate biopsies, other than those *scheduled* in the prostate biopsy substudy, will be left to the discretion of the clinical center's principal investigator."

Third Edition (Updated 03/10/97)

This update (dated, March 10, 1997) to the third edition of the protocol followed modifications to the protocol made during the Steering Committee meeting held on February 19, 1997. The update includes the following major changes to the third edition:

1) The Addition of the Prostatitis Questionnaire (Form Q04)

The Principal Investigators voted to implement the four question Prostatitis Questionnaire as recommended by the External Advisory Board.

Text of Amendment:

a) Added line 8 on page 13:
"3. Prostatitis Questionnaire (see Appendix H)."

b) Added line 30 on page 13 through line 1 on page 14:
"Baseline measurements from the health survey and prostatitis questionnaires will be taken during SV2."

c) Modified (noted in italics) lines 18-20 on page 16:
"The sexual function (see Appendix C), MOS-36 Health Survey (see Appendix D) and *Prostatitis (see Appendix H)* questionnaires will be administered yearly and at the last visit."

d) Added line 3 on page 21:
"4. Prostatitis Questionnaire"

e) Informed Consent Document Prototype in Appendix A, modified (noted in italics) the 3rd paragraph of "PROCEDURES":

"You will complete *four* questionnaires that determine the severity of your urinary symptoms, your sexual health, *and your quality of life*."

f) Modified the table in Appendix G:
In the All Participants section, added "Prostatitis Questionnaire" row

g) Added Appendix H: Prostatitis Questionnaire

2) Addition of Abbreviated Protocol for Bladder Cancer

The Principal Investigators voted to implement an abbreviated protocol for patients diagnosed with bladder cancer.

Text of Amendment:

a) Modified (noted in italics) the "Abbreviated Follow-up Protocol for Prostate Cancer" on page 17:
"2. Abbreviated Follow-up Protocol for Prostate *and Bladder* Cancer

... For participants with prostate *or bladder* cancer that are receiving a known therapy for their prostate cancer *or have any bladder-sparing procedure for their bladder cancer (e.g. TURBT)*, a simplified follow-up protocol will be initiated ... *For participants with bladder cancer that undergo a cystectomy for their bladder cancer, the abbreviated protocol will be limited to the MOS-36 Health Survey (see Appendix H) only, administered at annual follow-up visits.* Participants with prostate *or bladder* cancer that enroll in a prostate *or bladder* cancer study, *respectively,* will be handled ..."

3) Change in Proscar Labeling

Merck & Co., Inc. updated the Proscar label with the Federal Drug Administration to reflect some rarely occurring side effects and to remove the warning regarding semen exposure of pregnant women.

Text of Amendment:

a) Informed Consent Document Prototype in Appendix A, added to the end of the 4th paragraph of "RISKS":
"Other rarely occurring side effects include breast swelling and/or tenderness and allergic reactions such as lip swelling and rash."

b) Informed Consent Document Prototype in Appendix A, modified the 5th paragraph of "RISKS".

4) Miscellaneous

Text of Amendment:

a) Modified (noted in italics) line 10 on page 29:
" This committee *includes* ..."

Third Edition (Updated 07/03/97)

This update (dated, July 3, 1997) to the third edition of the protocol followed modifications to the protocol made during the Steering Committee meeting held on May 20, 1997. The update includes the following major changes to the third edition:

1) The Addition of Urosepsis to the Primary Outcome Definition

The Principal Investigators voted to add urosepsis to the definition of the primary endpoint.

Text of Amendment:

a) Added definition of Urosepsis Event in Appendix F:
"A single episode of urosepsis due to bladder outlet obstruction documented by positive culture."

b) Added (noted in italics) to line 13 on page 5:
"3. Recurrent urinary tract infections *or urosepsis* (defined in Appendix F)."

c) Added (noted in italics) to line 26 on page 5:
"Participants classified into category I (clinical progression of BPH) because of acute urinary retention, renal insufficiency due to BPH, recurrent urinary tract infections*, urosepsis* or incontinence will be taken off coded medication but will continue their scheduled follow-up visits, if possible."

2) Selected Medications were removed from the Exclusionary Medication List

The Principal Investigators voted to allow the use of selected serotonin uptake inhibitors.

Text of Amendment:

a) Added (noted in italics) to lines 4-9 on page 9:
"5. Taken phenylephrine, pseudoephedrine, imipramine, an anticholinergic or cholinergic medication within 4 weeks of the first screening visit, with the

exception of *the following:* topical anti-cholinergic eye drops used for glaucoma for more than 3 months prior to the first screening visit*, or one of the selected seratonin uptake inhibitors anti-depressants [Paroxetine HCl (Paxil), Fluoxetine HCl (Prozac) or Sertraline HCl (Zoloft)].*"

Third Edition (Updated 10/10/97)

This update (dated, October 10, 1997) to the third edition of the protocol followed modifications to the protocol made during the Steering Committee meeting held on September 23, 1997. The update includes the following major changes to the third edition:

1) The Discontinuation of the Urodynamics Substudy

The Steering Committee decided to discontinue the substudy due to lack of enrollment and feasibility. The External Advisory Board agreed with this decision. Therefore, the details of the substudy were removed from the protocol in the following places:

a) The substudy description (Section 3, Part E).

b) The study procedures (Section 6, Part B)

c) The case report form was removed from the Other Specific Forms listing (Page 20)

d) The subcommittee was removed from the list (Page 29)

2) Rechallenge of 8 mg doxazosin for patients who have previously decreased from 8 mg to 4 mg.

At the September 23, 1997 meeting, the Steering Committee voted to allow rechallenge of 8 mg of doxazosin for patients who decreased their maintenance dose from 8 mg to 4 mg at the investigator's discretion.

Text of Amendment:

a) Modified (noted in italics) lines 19-21 on page 15:
"Participants who decrease their dosage of doxazosin from 8 mg to 4 mg *may be rechallenged with the 8 mg dose at the discretion of the principal investigator.*"

3) New Case Report Forms

At the September 23, 1997 meeting, the Steering Committee voted to implement two new case report forms: PSA Collection Report and Missed Biopsy Report.

Text of Amendment:

a) Addition of line 4 on page 21:
"5. PSA Collection Report"

b) Addition of line 7 on page 21:
"8. Missed Biopsy Report"

Third Edition (Updated 2/25/98)

This update (dated, February 25, 1998) to the third edition of the protocol followed notification of a modification to the FDA Guidelines. This update includes the following change to the third edition:

1) Addition to the Definition of a Serious Adverse Event

Text of Amendment:

a) Addition of lines 25-30 on page 19:

"In accordance with the FDA Guidelines effective April 6, 1998, the following additional category is added to the definition:

6. important medical events that may not result in death, be life-threatening or require hospitalization if, based on appropriate medical judgement, they may jeopardize the patient and may require medical or surgical intervention to prevent a serious adverse event."

Third Edition (Updated 10/13/00)

This update (dated, October 13, 2000) to the third edition of the protocol followed the addition of case report forms and changes for End-of-Study. The update includes the following major changes to the third edition:

1) New Case Report Forms

The Executive Committee voted to implement two new case report forms: Prostate Cancer Registry Report and Prior Use of Viagra Report.

Text of Amendment:

a) Addition of line 14 on page 21:
"15. Prostate Cancer Registry Report"

b) Addition of line 15 on page 21:
"16. Prior Use of Viagra Report"

2) Addition of End of Study Procedures and Case Report Forms

a) The Steering Committee voted by ballot to add End-of-Study procedures.

Text of Amendment:

i) Addition of lines 11-16 on page 16:

"5. End of Study Medication

At the last follow-up visit scheduled within September 1, 2001 to November 30, 2001, finasteride (or its placebo) and doxazosin (or its placebo) will be dispensed to participants who elect to continue taking their coded medications for the duration of time between the last scheduled follow-up visit and the disclosure of final study results and treatment code assignments."

ii) Addition (noted in italics) of lines beginning on line 36, page 16:

" For participants of the biopsy of the prostate substudy, the following procedures are performed at 12 months post-randomization, at the time of the primary outcome (i.e., clinical progression of BPH) and *either at the 5-year follow-up visit or at* the last follow-up visit, *whichever occurs first*: transrectal ultrasound and needle biopsy of the prostate and collection of a serum sample for analysis of hormones. *Pilot study participants who are already beyond 5 years of follow-up at the time of implementation of this amended protocol but have not yet reached the last follow-up visit will have a transrectal ultrasound and needle biopsy of the prostate and collection of serum sample for analysis of hormones at the earliest possible scheduled follow-up visit.*

For non-participants of the biopsy of the prostate substudy, a transrectal ultrasound will be performed either at the 5-year follow-up visit or at the last follow-up visit, whichever occurs first.

Participants who elect to receive coded medications at the last follow-up visit scheduled within September 1, 2001 to November 30, 2001 will be assessed for adverse events at 3 months after the last scheduled follow-up visit, and for compliance to treatment regimen and adverse

events at a final separation visit. Unused coded medications will be returned to the clinic and treatment group assignment will be disclosed to the participant at the separation visit.

Participants who elect not to receive coded medications at the last follow-up visit will be scheduled for a final separation visit to disclose treatment group assignment."

b) The Steering Committee voted by ballot to implement two new case report forms for End-of-Study: Post End-of-Study Visit Inventory and Final Status Report for Inactive Participants.

Text of Amendment:

i) Addition of lines 16-18 on page 21:

"4. End-of-Study Forms

1. Post End-of-Study Visit Inventory

2. Final Status Report for Inactive Participants"

Third Edition Update: 10/13/00

Table of Contents

List of Abbreviations

Abbreviations	Definition
ALT	Alanine Aminotransferase Enzyme
AUA	American Urological Association
BCC	Biostatistical Coordinating Center
BPH	Benign Prostatic Hyperplasia
CBC	Complete Blood Count
CRF	Case Report Form
DHT	Dihydrotestosterone
DxC	Diagnostic Center
MOS-36	Medical Outcomes Study 36-Items Short Form Health Survey
MTOPS	Medical Therapy of Prostatic Symptoms
NIDDK	National Institute of Disease and Digestive and Kidney Diseases
NIH	National Institute of Health
PSA	Prostate-specific Antigen
PVR	Post Void Residual
RDM	Remote Data Management
SAS	Statistical Analysis Systems
SV0	Screening Visit 0
SV1	Screening Visit 1
SV2	Screening Visit 2
TRUS	Transrectal Ultrasound
QOL	Quality of Life

SECTION 1

Introduction

This protocol describes the National Institutes of Health (NIH) sponsored multi-center randomized clinical trial of the medical therapy of prostatic symptoms (MTOPS). The purpose of MTOPS is to determine the safety and efficacy of the pharmacotherapies finasteride (an inhibitor of 5-α-reductase) and doxazosin (a blocker of α-1 adrenoreceptors) on the clinical progression of BPH.

A. Primary Hypothesis

The primary hypothesis of this clinical trial is whether medical therapy (finasteride and/or doxazosin) delays or prevents the clinical progression of benign prostatic hyperplasia (BPH).

B. Purpose of the Study Protocol

The protocol for MTOPS describes the background, design and organization of the study. The protocol may be viewed as a written agreement among the study investigators, the participants, and the medical and scientific community (Friedman, Furberg, and DeMets, 1985).

The protocol was written by the Steering Committee for MTOPS, produced by the trial's Biostatistical Coordinating Center (BCC), and approved by the Institutional Research and Review Board of each participating clinical center prior to the initiation of recruitment. All changes to the protocol during the trial require the approval of the Steering Committee.

The protocol serves as an outline of MTOPS. All study procedures are presented in detail in the trial's Manual of Operations.

SECTION 2

Background of the Study

Relatively little is known about the causes of benign conditions affecting the prostate. Given the extent of disease in the prostate and the fact that nearly 400,000 transurethral prostatectomies are performed each year for relief of prostatic obstructive symptoms (Mebust, et al., 1989) it is remarkable that so little interest in the past has been dedicated to BPH by researchers, clinicians, and epidemiologists. In recent years, however, anatomical and physiological studies of the prostate have begun to provide information about the mysteries of this gland. A surge in interest for both invasive and non-invasive techniques of treatment has focused particular attention on the medical management of BPH.

The major factor determining the occurrence of BPH is age. Histological demonstration of this disorder has been shown to rise rapidly after age 40 with nearly 90% of men over the age of 80 having evidence of BPH (Berry, et al., 1984). The occurrence of this entity by itself does not necessarily correlate with the presence of clinical symptoms nor the need for surgical intervention. Nonetheless, it has been estimated that between 30 to 40% of 40 year old men will require prostate surgery for obstructive symptoms by the time they reach the age of 80 (Barry, 1990). Epidemiological research into other determinants of BPH has been scarce. There are no solid data to suggest an association of BPH with diet, smoking, caffeine, frequency of sexual intercourse, medications, or other diseases (Barry, 1990).

Very little is also known about racial factors in BPH and its treatment. While some studies have found that the age-specific autopsy prevalence of BPH is similar in a number of different countries (Isaacs and Coffey, 1989; Bostwick, et al., 1992), much less is known about the age-specific prevalence of clinically diagnosed BPH. This is principally because widely accepted clinical diagnostic criteria suitable for use in epidemiologic studies do not exist. Hence it is difficult to determine how much of the variation in prevalence of BPH is due to differences between the populations studied and how much is due to differences in the diagnostic criteria (Guess, 1992).

Sidney, et al. (1991) compared the incidence of surgically treated BPH among 2175 blacks and 12,722 whites who were followed from 1971 to 1987. The age-adjusted relative risk for blacks relative to whites was 1.0 (95% confidence interval: 0.8-1.2). The incidence of BPH tended to be slightly higher in blacks until age 65, after which it was higher in whites. The study was conducted among enrollees in a health maintenance organization where one would not expect racial differences in access to medical care. It is interesting to note that similar findings resulted from a study nearly 60 years earlier (Derbes, Leche, and Hooker, 1992).

The number of blacks enrolled in a recently completed study of finasteride among men with BPH was not sufficient to permit detection of any possible racial differences (Gormley, et al., 1992). Ongoing clinical trials of finasteride in the treatment

of BPH have provided for increased enrollment of blacks. Results from these studies are not yet available. However, it appears from what is known about the epidemiology of BPH that the age-specific incidence of clinically diagnosed and treated BPH should be roughly as common in blacks as in whites, in settings where there is equal access to health care.

Symptoms of BPH are the major impetus for patients to seek treatment and their severity frequently determines whether intervention is warranted. The symptomatology of BPH is complex because the size of the prostate frequently does not correlate well with severity of symptoms. Therefore, men with large palpable prostates may not experience significant symptoms nor elect treatment. On the other hand, men with small prostates may have severe symptoms.

Objective and subjective parameters have been used to measure patient response to treatment. Subjective measures usually consist of a symptom score designed to quantify the degree of obstruction based on its trouble to the patient. Symptom score is useful, but the variable impact of an individual symptom on each patient limits this method of measurement. For example, frequency of urination may not be nearly as bothersome to one patient as incomplete emptying, while the converse may be true for the next patient. The most commonly used objective parameter is urinary flow rate. Providing bladder function is not compromised, low urinary flow rates suggest bladder outlet obstruction while high rates suggest the opposite, especially at extremes of the scale. Although flow rates provide a means to measure the reduction of resistance before and after treatment, several investigators have demonstrated that patient satisfaction with treatment may not correlate well with objective response (Herbison, Fraundorfer, and Walton, 1988).

There are a few well-defined indications for surgical intervention in prostatic obstruction. Treatment is also indicated when chronic outflow obstruction has resulted in bladder decompensation and overflow incontinence. Other indications for rather prompt surgical intervention include patients with more than one episode of acute urinary retention, multiple urinary tract infections, and the rare patient with severe hematuria related to BPH. Although conventional wisdom holds that intervention is indicated for large post void residual urine volumes, no data exists about the natural history of these patients.

State-of-the art technology such as laser prostatectomy and microwave thermal therapy are currently under investigation as BPH treatment options. To date, randomized clinical trials have not been done to demonstrate the efficacy of these approaches. In contrast, two classes of medical therapy have been evaluated in short-term randomized clinical trials. Both α-1 adrenergic receptor blockade and 5-α-reductase inhibition are rational BPH treatment options. Short-term trials have demonstrated the efficacy of these approaches over placebo. However, there are presently no data to prove that medical therapy inhibits progression of the disease or decreases the probability of future prostatectomy.

With the recognition that a significant component of the prostatic stroma is smooth muscle and that the ratio of stroma to epithelium in BPH increases 2-1/2 times

over normal prostate tissue, inhibition or relaxation of this smooth muscle has become a goal for the BPH medical therapy. The potential for selective treatment of the prostate by α-1 adrenergic receptor blockade is suggested by the much greater density of α-1 adrenergic receptors in the bladder neck and prostate than in the detrusor (Lepor, et al., 1988). The first medication in this class tested in clinical trials was phenoxybenzamine, a non-selective α-adrenergic receptor antagonist (Caine, Perlberg, and Meretyk, 1978). Modest symptomatic responses were reported, but patients were plagued by dizziness, visual accommodation difficulties, and both congestion and dryness of the nasal passages. The introduction of more selective adrenergic receptor antagonists renewed interest for this pharmaceutical approach to BPH treatment.

Prazosin, a selective α-1 adrenergic receptor antagonist, is much better tolerated than phenoxybenzamine. Although the initial study did not show a great improvement in either subjective or objective parameters from placebo patients, subsequent studies have shown such an improvement (Kirby, et al., 1987). Patients with frequency and nocturia seem to be especially benefitted by this medication. The limitation of multiple daily dosage with prazosin due to a short half-life has been overcome with introduction of the newest selective α-1 adrenergic receptor antagonists, terazosin and doxazosin. These agents have demonstrated treatment efficacy in BPH over that seen by placebo (Lepor, Henry, and Laddu, 1991). Side effects include asthenia, orthostasis, and headache, but are relatively minor assuming careful dose titration.

BPH is an androgen dependent process. Medical and surgical castration is known to produce some involution in the size of the hyperplastic prostate (McConnell, 1990). Following medical castration with luteinizing hormone releasing hormone analogs, the prostate decreases in size by approximately 20 to 30 percent. However, only one-third of patients enjoy significant clinical improvement. More importantly, any type of androgen withdrawal which significantly lowers plasma testosterone seriously impairs libido and leads to sexual dysfunction. Medical castration approaches are not attractive as long-term treatment options.

The medication that has received the most interest lately is the 5-α-reductase inhibitor finasteride. Dihydrotestosterone (DHT) is the most potent intraprostatic androgen, primarily because DHT has a higher affinity for the androgen receptor in the prostate and this DHT-receptor complex may be more stable than the corresponding testosterone receptor complex. DHT inhibition also does not interfere with the peripheral effects of testosterone. Therefore, DHT inhibition is an attractive target for BPH pharmacotherapy. Two large-scale phase III clinical trials have demonstrated that finasteride produces a 20 percent reduction in prostatic volume and modest improvement in symptoms and maximal urinary flow rate (Gormley, et al., 1992). Side effects are limited to a 3 to 4 percent incidence of decreased libido, impotency, or ejaculatory disorders.

In summary, there is accumulating evidence to suggest that pharmacotherapy may be an appropriate alternative to surgery in some cases of BPH.

SECTION 3

Objectives

A. Primary Research Questions

The primary objective of MTOPS is to ascertain if medical therapy (finasteride and/or doxazosin) delays or prevents the progression of BPH. The primary outcome will be the time to clinical progression of BPH. Participants will be classified into one of four categories:

I. Clinical progression of BPH, as defined by one of the following:

1. Acute urinary retention (defined in Appendix F).
2. Renal insufficiency due to BPH, as indicated by a 50% increase from baseline in serum creatinine to at least 1.5 mg/dL confirmed within 4 weeks.
3. Recurrent urinary tract infections or urosepsis (defined in Appendix F).
4. Incontinence (defined in Appendix F).
5. An increase from baseline in the AUA symptom score index of 4 or more points confirmed 2 to 4 weeks later.

II. Crossover to known invasive therapy, prior to clinical progression (as defined in category I).

III. Non-compliance with the coded medication treatment regimen, including participants who elect watchful waiting or open-labeled medical therapy including inhibitor of 5-α-reductase or blocker of α-1 adrenoreceptors.

IV. Completion of study.

Participants classified into category I (clinical progression of BPH) because of acute urinary retention, renal insufficiency due to BPH, recurrent urinary tract infections, urosepsis or incontinence will be taken off coded medication but will continue their scheduled follow-up visits, if possible. Participants classified into category I because of an increase in the AUA symptom score will be taken off coded medication at the discretion of the clinical center's principal investigator but will continue their scheduled follow-up visits, if possible. Participants classified into category II (crossover to known invasive therapy) will be taken off coded medication but will continue their scheduled follow-up visits, if possible. Participants classified into category II prior to clinical progression of BPH (category I) will remain classified as category II (i.e., never be classified into category I). Participants classified into category III (non-compliance with

the coded medication) will continue to be followed, if possible, and will eventually be classified into either categories I, II, or IV by the end of the trial.

The primary analysis will be the time to clinical progression of BPH (i.e., time to category I). Participants in categories II through IV at the end of the trial will be censored as of the date of their last completed visit. A supportive analysis will be the time to the first occurrence of clinical progression of BPH (category I) or crossover to known invasive therapy (category II). For this analysis, participants in categories III or IV at the end of the trial will be censored as of the date of their last completed visit.

B. Secondary Research Questions

Although time to clinical progression of BPH is the primary outcome of the study, a key secondary objective of the study will include an assessment of:

1. The natural history of BPH in a well-defined cohort of men.

Other secondary objectives of the study will include assessing differences over time between the four treatment groups with regard to:

2. AUA symptom score and impact index
3. Medical Outcomes Study (MOS) 36-Item Short Form Health Survey score
4. Maximal uroflow

C. Subgroup Hypotheses

Other hypotheses concern whether treatment response or progression of disease in the placebo and three treatment arms are the same or different in subgroups classified by:

1. AUA symptom score and impact index
2. MOS-36 Health Survey score
3. Maximal uroflow
4. Residual urine
5. Prostate volume

D. Substudy - Ultrasound, Biopsy of the Prostate and Hormones

A key feature of this protocol is the inclusion of predetermined tissue biopsies that will be obtained to evaluate the status of the prostate before and after medication in approximately half of the randomized participants. During the biopsy of the prostate, the participants will undergo transrectal ultrasound (TRUS) of the biopsy to assess differences over time between the four treatment groups with regard to prostate

volume. In addition, a serum sample will be forwarded to the diagnostic center for analysis of hormones (testosterone, dihydrotestosterone, and luteinizing hormone).

The purpose of this substudy is to provide additional information regarding the histopathobiology of BPH and to test the existing biomarkers for their prognostic ability regarding response to therapy. Specific studies to be carried out can be divided according to phases of BPH development as follows:

1. Proliferation: Immunohistochemical localization of MIB-1 nuclear proliferation antigen.

2. Differentiation: Immunohistochemical localization of basal cell specific cytokeratin, pancytokeratin, and smooth muscle action; stromal/epithelial ratio will be determined by video-image analysis.

3. Biosynthesis: Immunohistochemical localization of prostate-specific antigen; morphometric analysis of epithelial cell height.

4. Atrophy: In situ terminal deoxynucleotidyl transferase determination of apoptotic cell death.

This list is likely to be modified during the course of the trial as new or additional markers become available. In addition, an attempt will be made to correlate histopathologic changes of the peripheral zone with concurrent changes in the transition zone with the eventual goal of establishing a cause-effect relationship.

Approximately half of the randomized participants will undergo TRUS and biopsy of the prostate with the collection of a serum sample for analysis of hormones. All potential participants undergoing initial evaluation for study eligibility will have TRUS and biopsy presented to them as an important aspect of the clinical trial. Only those participants who refuse to undergo biopsy of the prostate will be offered the option of participation without biopsy. During the initial screening visit, biopsy will not be presented as an "optional test".

SECTION 4

Study Design

A. Overall Design

MTOPS is a multi-center randomized, placebo-controlled, double-masked clinical trial in which eligible participants with BPH will be randomly assigned to either of three drug treatment arms or a placebo control. Participants will be followed for a minimum of four and a maximum of six years, with an average follow-up of five years, assuming uniform recruitment.

Preceding the full-scale clinical trial a pilot study was conducted to assess the feasibility of the full-scale trial. For the pilot study, 141 participants were recruited in six clinical centers and were followed for an average of six months (range: 2 to 10 months).

B. Eligibility Criteria

Potential participants meeting the following criteria will be eligible for randomization:

1. Male at least 50 years of age.

2. Peak urinary flow rate is at least 4 ml/sec, but not greater than 15 ml/sec, and the voided volume is at least 125 ml.

3. AUA symptom severity score is greater than or equal to 8 and less than or equal to 30.

4. Voluntarily signed the informed consent agreement prior to the performance of any study procedures.

C. Exclusion Criteria

Potential participants with any of the following will be excluded from the full-scale trial:

1. Any prior intervention for BPH (either medical or surgical).

2. Received any prior experimental intervention for prostate disease (either medical or surgical) or is presently enrolled in any study protocol.

3. A previous hypersensitivity, idiosyncrasy, or clinically suspected drug reaction to α-blockers, quinazoline compounds, or finasteride.

4. Taken an α-1 blocker for hypertension within a year of randomization.

5. Taken phenylephrine, pseudoephedrine, imipramine, an anticholinergic or cholinergic medication within 4 weeks of the first screening visit, with the exception of the following: topical anti-cholinergic eye drops used for glaucoma for more than 3 months prior to the first screening visit, or one of the selected serotonin uptake inhibitors anti-depressants [Paroxetine HCl (Paxil), Fluoxetine HCl (Prozac) or Sertraline HCl (Zoloft)].

6. Taken an estrogen, androgen, or any drug producing androgen suppression, or anabolic steroids. If the patient has taken prescription cimetidine within 3 months prior to the first screening visit.

7. An inability to urinate.

8. Supine blood pressure of less than 90/70 mmHg.

9. Clinically significant renal or hepatic impairment (i.e., creatinine greater than 2.0 mg/dL or ALT greater than 1.5 times the upper limit of normal).

10. Serum prostate specific antigen level greater than 10 ng/ml.

11. Requires the daily use of a pad or device for incontinence.

12. An episode of unstable angina pectoris, a myocardial infarction, transient ischemic attack, or a cerebrovascular accident within the past six months.

13. Orthostatic hypotension, or a history of significant fainting spells or blackouts. Orthostatic hypotension is defined as a decrease in the systolic blood pressure of greater than 20 mmHg or a decrease in the diastolic blood pressure of greater than 10 mmHg between the supine and standing positions, or the development of significant postural symptoms.

14. History or current evidence of carcinoma of the prostate or bladder, pelvic radiation or surgery, urethral stricture, prior surgery for BPH or bladder neck obstruction.

15. Active urinary tract disease or has undergone cystoscopy or biopsy of the prostate within one month prior to the first screening visit or has an imminent need for surgery.

16. Known primary neurologic conditions such as multiple sclerosis or

Parkinson's disease or other neurological diseases known to affect bladder function.

17. Documented bacterial prostatitis within the past year.

18. Two documented urinary tract infections of any type in the past year.

19. Severe bleeding disorder which makes a biopsy impossible.

20. Cancer which is not considered cured (except basal cell or squamous cell carcinoma of the skin). A potential participant is considered cured if there has been no evidence of cancer within five years of randomization. Evidence of bladder cancer or prostate cancer is exclusionary whether the patient is considered cured or not.

21. Diagnosis of a thought disorder (i.e., schizophrenia, bipolar disorder).

22. History of alcoholism or any other substance abuse which, in the opinion of the investigator, would affect compliance with the protocol.

23. Any serious medical condition likely to impede successful completion of the long-term study.

D. Treatment Group

Participants will be randomized, double-masked, to one of four treatment groups:

1. Finasteride and a doxazosin placebo.
2. Doxazosin and a finasteride placebo.
3. Both doxazosin and finasteride.
4. A finasteride placebo and a doxazosin placebo.

E. Assignment to Treatment Groups

1. Stratification

Randomization will be stratified by clinical center. Pre-stratification by clinical center will ensure balance between the four treatment groups with respect to anticipated differences in the participant populations and possible differences in participant management.

2. Randomization Method

There are several alternative methods to randomly assign the participants within clinical center (e.g., simple randomization or permuted block designs). The urn method of randomization provides a high probability of balance in treatment assignments, is unpredictable, and allows an explicit randomization analysis to be conducted with relative ease (Wei and Lachin, 1988). For these reasons, the urn method will be used to randomly assign participants to the four treatment groups.

A sequence of randomization numbers within a clinical center will be constructed of the form XXYYY, where XX is the clinical center number and YYY is the unique three digit participant number. The BCC will prepare the master randomization list with assignments of the two treatment groups to the randomization number within a clinical center using the standard urn design.

The randomization list with treatment group assignments will be forwarded, in confidence, to the drug distribution center for drug labeling and distribution. At no time will the code of the medication be broken without the express knowledge and consent of the clinical center's Principal Investigator.

If, however, there is a serious adverse event which is thought by the clinical center staff to be possibly or probably related to the coded medication, the clinical center staff, when necessary for the safety of the participant, will unmask treatment group assignment upon conferring with the clinical center's principal investigator. In this event, the clinical center staff must promptly contact the BCC with an explanation of the need for unmasking the treatment group assignment. A detailed written report must also be submitted to the BCC within three working days of the initial BCC contact.

3. Level of Masking

MTOPS will be double-masked. Neither the participants nor the participant's care-givers will be aware of the treatment assignments. Treatment assignment codes will be known only by the staff of the BCC and the drug distribution center.

SECTION 5

Randomization of Participants

A. Informed Consent

Prior to screening visit #1 (SV1), potential participants will undergo pre-screening procedures (e.g., chart review, telephone interview) to identify candidates for screening visits; this pre-screening is identified as SV0. If a potential participant is identified during SV0, the SV1 will be scheduled. During SV1, the trial and procedures will be thoroughly explained and the participant will be asked to sign an informed consent form. The informed consent form developed by the Steering Committee will be used as a model (See Appendix A). Each center will develop its own modifications based on the requirements of its own institutional review board.

B. Screening for Eligibility

During SV1, after the participant has signed the informed consent document, the participant will undergo the following procedures to determine eligibility:

1. The AUA symptom score, impact index, and quality of life (QOL) questionnaires will be administered (see Appendix B).

2. The sexual function questionnaire will be administered (see Appendix C).

3. Vital signs.

4. Assessment of urinary flow rates and post-void residual (PVR; see Manual of Operations for details).

5. Three serum samples will be taken (prior to the digital rectal exam). Two will be forwarded to the diagnostic center, one for analysis of prostate-specific antigen (PSA) and one for the serum bank. The third sample will be kept by the clinical center for a complete hematology and serum chemistry analysis (see Appendix E for details of the hematology/chemistry analysis).

6. Physical exam (including digital rectal exam) and urinalysis (see Appendix E for details).

7. Medical history.

8. Tracking information (patient information and recruitment source).

If the participant successfully satisfies the inclusion/exclusion criteria based on the measurements taken during SV1, he will be scheduled for screening visit #2 (SV2). During SV2, the following procedures will be performed:

1. The AUA symptom score, impact index, and quality of life (QOL) questionnaires will be administered (see Appendix B).

2. MOS-36 Health Survey (see Appendix D).

3. Prostatitis Questionnaire (see Appendix H).

4. Vital signs.

5. Assessment of urinary flow rates and post-void residual (PVR; see Manual of Operations for details).

6. Transrectal ultrasound (TRUS).

For participants of the biopsy of the prostate substudy, the following procedures will also be performed during SV2:

7. One serum sample will be taken and forwarded to the diagnostic center for analysis of hormones (testosterone, dihydrotestosterone, and luteinizing hormone).

8. Needle biopsy. Tissue samples will be forwarded immediately to the diagnostic center for analysis.

All participants will then be put on a two-week run-in period. The participant will be given coded medication and instructed to take it for a two-week period. Following the run-in period, if the participant is not excluded from the study, he will be scheduled for a randomization visit. At this visit, only vital signs will be obtained.

The screening period (from SV1 to the randomization visit) will not exceed 6 weeks, including the two-week run-in period. If a potential participant is not randomized within 6 weeks after SV1, the participant must reenter the screening period in order to be considered eligible for randomization.

C. Baseline Evaluation

Baseline measurements from the serum samples and sexual function questionnaire will be taken during SV1. Baseline measurements from the health survey

and prostatitis questionnaires will be taken during SV2. Baseline urinary flow rate, PVR, symptom score, and vital signs will be taken during SV2 (measurements taken during SV1 will be used only for inclusion/exclusion criteria). Measurements taken at the randomization visit will not be used because of their proximity to the potentially biasing invasive procedures.

D. Allocation to Treatment Groups

Following a successful baseline period, the participant will be officially randomized. Random assignment of a participant to a treatment arm will use the microcomputer-based randomization component of the remote data management (RDM) system. The participant is officially randomized when the RDM system discloses the participant's five-digit randomization number.

E. Modifying Recruitment Based on Monitoring Prostate Volumes

All randomized participants will have a transrectal ultrasound (TRUS) of the prostate during screening visit #2. Based on this TRUS, the ellipsoid volume of the total gland (in cc) will be recorded and forwarded to the BCC using the remote data management system. The proportion of randomized participants with prostate volumes < 20 cc and > 50 cc will be reviewed by the Recruitment and Retention Subcommittee after 500, 1,000 and 1,500 participants have been randomized. Based on this periodic review, the Subcommittee may modify the recruitment procedures using the following criteria

1. If the lower 99% confidence limit on the proportion of prostate volumes < 20 cc is greater than 0.25 then the number of randomized participants with prostate volumes < 20 cc will be restricted as follows: each clinical center will be required to randomize no more than one participant with a baseline prostate volume < 20 cc for every 5 randomized participants.

2. If the lower 99% confidence limit on the proportion of prostate volumes > 50 cc is greater than 0.25 then the number of randomized participants with prostate volumes > 50 cc will be restricted as follows: each clinical center will be required to randomize no more than one participant with a baseline prostate volume > 50 cc for every 5 randomized participants.

3. If the upper 99% confidence limit on the proportion of prostate volumes > 50 cc is less than 0.15 then the number of randomized participants with prostate volumes > 50 cc will be enriched as follows: each clinical center will be required to randomize at least one participant with a baseline prostate volume > 50 cc for every 5 randomized participants.

SECTION 6

Study Procedures

A. Medical Treatment Protocol

1. Dosing Schedule

All randomized participants will be prescribed 5 mg of finasteride (or its placebo) once per day, at bedtime.

All randomized participants will also be prescribed doxazosin (or its placebo) which must be titrated to determine participant tolerance. At randomization, participants will be given 1, 2 and 4 mg doses of coded doxazosin medication. At randomization, participants will be prescribed a 1 mg dose level; at end-week 1, the participant will be prescribed a 2 mg dose; and at end-week 2, the participant will be prescribed a 4 mg dose. At the end-week 3 visit, the participant will be given an 8 mg dose. The participant's final tolerated dosage will be administered at the end-week 4 visit. Only those participants tolerating a 4 or 8 mg dose (or its placebo) will be kept on doxazosin (or its placebo) in the study. The final dosage will be administered once per day, at bedtime. Participants who discontinue the doxazosin treatment regimen for greater than 3 days will be required to undergo a new titration period to determine maximal dosage. Multiple doxazosin titration periods will be allowed for each participant in the study. Participants who decrease their dosage of doxazosin from 8 mg to 4 mg may be rechallenged with the 8 mg dose at the discretion of the principal investigator.

2. Measures of Compliance

Participants will be instructed to bring their packaged coded medication at each follow-up visit. Pill counts will be conducted to assess the participant's level of compliance with the medical treatment regimens.

3. Packaging of Medications and Supplies

For the full-scale trial, finasteride (or its placebo) will be packaged centrally by the pharmaceutical manufacturer in bottles and forwarded to the drug distribution center for labeling and distribution directly to the clinical center with the participant's five-digit randomization number on the label.

Doxazosin (or its placebo) will be shipped in bulk by the pharmaceutical manufacturer to the drug distribution center for packaging, labeling and distribution directly to the clinical center with the participant's five-digit randomization number on the label. One titration pack will be packaged for each participant. Each participant will receive both 4 mg and 8 mg bottles, so that the dosage can be reduced from 8 mg to 4

mg if warranted during the course of the study.

Clinical monitors will make site visits to each of the clinical centers during the full-scale trial, in order to ascertain whether proper drug storage and accounting procedures are being maintained.

4. Masking Procedure and Labeling

In order to preserve the double-masking of the trial, only the BCC and the drug distribution center will be unmasked. The drug distribution center will be provided with the randomization sequence and treatment assignment directly by the BCC. All labeling will be homogeneous among clinics and participants, and will include only the five-digit randomization number of the participant.

5. End of Study Medication

At the last follow-up visit scheduled within September 1, 2001 to November 30, 2001, finasteride (or its placebo) and doxazosin (or its placebo) will be dispensed to participants who elect to continue taking their coded medications for the duration of time between the last scheduled follow-up visit and the disclosure of final study results and treatment code assignments.

B. Follow-up Protocol

Measurements will be collected prospectively through the study at 3 month intervals (except for the first month of follow-up when dose titration of doxazosin will require visits at end-weeks 3, and 4). Serum samples will be taken at 12 months, yearly thereafter, and at the last visit for PSA, chemistry, and hematology analysis (see Appendix E for details of hematology and chemistry analyses). A physical exam and urinalysis (see Appendix E) will be performed yearly and at the last visit. The sexual function (see Appendix C), MOS-36 Health Survey (see Appendix D) and Prostatitis (see Appendix H) questionnaires will be administered yearly and at the last visit. Appendix G gives a follow-up schedule for the full-scale clinical trial.

If the participant does not continue in the study, a major follow-up visit will be conducted at the last patient visit.

During titration visits (e.g., end-weeks 3 and 4), the participant will be examined for vital signs, and will be assessed for compliance to treatment regimen and for adverse events. At each 3-month assessment point, the participant will be examined for vital signs, will receive the AUA symptom questionnaire (Appendix B), will have an analysis of flow rate, and will be assessed for compliance to treatment regimen and for adverse events.

For participants of the biopsy of the prostate substudy, the following procedures are performed at 12 months post-randomization, at the time of the primary outcome

(i.e., clinical progression of BPH) and either at the 5-year follow-up visit or at the last follow-up visit, whichever occurs first: transrectal ultrasound and needle biopsy of the prostate and collection of a serum sample for analysis of hormones. Pilot study participants who are already beyond 5 years of follow-up at the time of implementation of this amended protocol but have not yet reached the last follow-up visit will have a transrectal ultrasound and needle biopsy of the prostate and collection of serum sample for analysis of hormones at the earliest possible scheduled follow-up visit.

For non-participants of the biopsy of the prostate substudy, a transrectal ultrasound will be performed either at the 5-year follow-up visit or at the last follow-up visit, whichever occurs first.

Participants who elect to receive coded medications at the last follow-up visit scheduled within September 1, 2001 to November 30, 2001 will be assessed for adverse events at 3 months after the last scheduled follow-up visit, and for compliance to treatment regimen and adverse events at a final separation visit. Unused coded medications will be returned to the clinic and treatment group assignment will be disclosed to the participant at the separation visit.

Participants who elect not to receive coded medications at the last follow-up visit will be scheduled for a final separation visit to disclose treatment group assignment.

1. Discontinuation of the Follow-up Protocol

The occurrence or presence of the following will constitute discontinuation of the scheduled follow-up protocol:

1. Inactive follow-up. (a) Voluntary withdrawal by the participant, or (b) any condition which, in the opinion of the principal investigator, makes it unsafe for the participant to continue.

2. Death.

2. Abbreviated Follow-up Protocol for Prostate and Bladder Cancer

Randomized participants with a diagnosis of prostate cancer who elect "watchful waiting" will continue their coded medication and scheduled follow-up visits. For participants with prostate or bladder cancer that are receiving a known therapy for their prostate cancer or have any bladder-sparing procedure for their bladder cancer (e.g. TURBT), a simplified follow-up protocol will be initiated. This abbreviated follow-up protocol will be limited to the AUA symptom questionnaire (Appendix B) administered at quarterly follow-up visits and the MOS-36 Health Survey (Appendix D) administered at annual follow-up visits. For participants with bladder cancer that undergo a cystectomy for their bladder cancer, the abbreviated protocol will be limited to the MOS-36 Health Survey (see Appendix H) only, administered at annual follow-up visits. Participants with prostate or bladder cancer that enroll in a prostate or bladder cancer study,

respectively, will be handled on a case-by-case basis by the Clinical Review Subcommittee.

C. Participant Management Protocols

1. Blood Pressure Control

Because of the antihypertensive effect of doxazosin, it is important that participant blood pressure be adequately monitored. Participants will also be assessed for orthostatic hypotension based on supine and standing blood pressure. Orthostatic hypotension is defined as a decrease in the systolic blood pressure of greater than 20 mmHg or a decrease in the diastolic blood pressure of greater than 10 mmHg between the supine and standing positions, or the development of significant postural symptoms.

2. Prostate Specific Antigen

Serum prostate specific antigen (PSA) assays will be performed by the Diagnostic Center at baseline, 12 months and yearly thereafter. The baseline serum PSA collected at screening visit #1 (SV1) will be reported directly back to the corresponding clinical center to determine participant eligibility and need for biopsies prior to randomization.

Follow-up PSA values will be reported by the Diagnostic Center directly to the Biostatistical Coordinating Center (BCC) where the BCC will apply a correcting algorithm prior to reporting the PSA value to the corresponding clinical center. The correction algorithm will be: (1) for participants on placebo or doxazosin only, the PSA value will be multiplied by one and (2) for participants on finasteride only or finasteride plus doxazosin, the PSA value will be multiplied by two plus a correction factor for odd-numbered values. Both the Diagnostic Center and individual clinical centers will remain masked to treatment assignment.

Decisions based on the PSA value concerning the need for additional prostate biopsies, other than those scheduled in the prostate biopsy substudy, will be left to the discretion of the clinical center's principal investigator.

3. Treatment Emergent Adverse Events

Reporting of adverse events will be accomplished by collecting information on adverse experiences at each follow-up visit. Occurrence of an adverse event will be indicated on the standard follow-up visit case report form and detailed on the adverse event report form.

In order to facilitate timely reporting of certain serious adverse events, the Adverse Event Report will be filled out immediately and directed to the BCC, where the BCC medical consultant will serve as the serious adverse event report monitor. It is important to note that all serious adverse events should be reported in this way,

regardless of whether the adverse event is suspected to be related to study medication. A "serious" adverse event is defined as one which is:

1. fatal or life threatening
2. permanently disabling
3. requiring or prolonging inpatient hospitalization
4. a congenital anomaly or cancer
5. an overdose

In accordance with the FDA Guidelines effective April 6, 1998, the following additional category is added to the definition:

6. important medical events that may not result in death, be life-threatening or require hospitalization if, based on appropriate medical judgement, they may jeopardize the patient and may require medical or surgical intervention to prevent a serious adverse event.

SECTION 7

Data Processing

A. Case Report Forms (CRFs)

Case report forms will be filled out at each visit to collect participant data.

1. Baseline Forms

1. Eligibility/Exclusion Inventory
2. Screening Visit 1: Medical History, Vital Signs, Physical Examination, Urinary Flow Rates, Local Laboratory Results (Urinalysis and Hematology/Chemistries).
3. Screening Visit 2: Vital Signs and Urinary Flow Rates.
4. Randomization Visit: Vital Signs.
5. Recruitment Source Tracking

2. Follow-up Forms

1. Standard Follow-up Visit Inventory: Vital Signs, Urinary Flow Rates, Compliance, Adverse Events, and Concomitant Medications (administered at every participant visit except for titration visits)
2. Major Follow-up Visit Inventory: Physical Examination and Local Laboratory Results (administered yearly)
3. Interim Visit Checklist: Vital Signs, Compliance, and Intercurrent Illness.
4. Missed Follow-Up Visit Report
5. Titration Visit Inventory: Vital Signs, Compliance, Adverse Events (administered at end-weeks 3 and 4 of any titration period)

3. Other Specific Forms

1. AUA Symptom Questionnaires

2. Sexual Function Questionnaire
3. MOS-36 Health Survey Questionnaire
4. Prostatitis Questionnaire
5. PSA Collection Report
6. TRUS/Biopsy Data
7. Non-scheduled Biopsy Information
8. Missed Biopsy Report
9. Significant Clinical Events
10. Adverse Event Report
11. Patient Tracking Information
12. Medication Run-In Information
13. Clinic Laboratory Normal Range Report
14. Clinic Review Committee Report
15. Prostate Cancer Registry Report
16. Prior Use of Viagra Report

4. End-of-Study Forms

1. Post End-of-Study Visit Inventory
2. Final Status Report for Inactive Participants

The case report forms are created centrally at the BCC and sent to the clinics. The clinic coordinators fill out the forms and enter them into the local microcomputer. The forms will be edited as they are entered into the microcomputer-based remote data management system.

B. Remote Data Management System

1. Clinical Centers

The microcomputer remote data management system consists of a network of microcomputers, one at each clinical center and one at the BCC. Hardware includes Dell microcomputers and auto-answer, auto-dial modems. Data entry software corresponding to the CRFs completed at a clinical center will be developed and maintained by the staff at the BCC. Data will be entered by clinical center staff and transmitted weekly via telecommunications link to the BCC.

2. Diagnostic Center

A single microcomputer will be located at the Diagnostic Center, which will include a Dell microcomputer and an auto-answer, auto-dial modem. Data entry software corresponding to the analyses performed at the Diagnostic Center will be developed and maintained by the staff at the BCC. Data will be entered by diagnostic center staff and transmitted weekly via telecommunications link to the BCC.

C. Centralized Data Management System

Data will be transmitted weekly from the clinical centers and the Diagnostic Center to the BCC and uploaded to the mainframe and converted to SAS data sets. All new data will be edited weekly for unavailable, out of range, or inconsistent values. Monthly audit programs will produce more detailed edits across all forms for an individual participant. Summaries will be prepared for reports to the Steering Committee.

D. Performance Monitoring

1. Training Workshop and Site Visits

The BCC will establish procedures to train and certify clinical investigators in the MTOPS protocol and data processing procedures. Prior to the initiation of recruitment for the full-scale clinical trial, a workshop will be held at which time the personnel from the clinical centers will be trained in the appropriate study procedures including the use of the case report forms and data processing systems. At that time, Diagnostic Center personnel will instruct the coordinators on proper packaging and mailing of specimens for analysis by the Diagnostic Center. The BCC will maintain close contact with the clinic coordinators and will provide additional training or review as needed.

In addition to a training workshop, each of the clinical centers will be visited by clinical monitors. Appropriate representatives from the BCC, the Diagnostic Center, the NIDDK, and other experts will visit the clinical centers, as required. These site visits will review procedures with the clinic coordinators/technicians, assess proficiency in executing the study protocol, review deficiencies detected in monitoring the

performance of the clinical centers, review the utilization of personnel relative to the amounts budgeted, and receive feedback on the adequacy of the centralized support operations.

2. Periodic Performance Reports

During the full-scale clinical trial, the BCC will monitor the performance of the clinical centers and produce periodic reports summarizing protocol performance.

a. Recruitment

The performance of the clinical centers in recruiting eligible BPH participants will be carefully monitored by the BCC. Monthly recruitment summaries will be issued to the Steering Committee throughout the recruitment and randomization period showing the number of potential participants screened, number randomized, and reasons for ineligibility or refusal to participate by clinical center. The reasons for ineligibility will be compared among the clinical centers, and if large differences are found, explanations for these differences will be sought. If the randomization rate falls below the desired number of participants per month, data on reasons for ineligibility and refusal will be used to try to identify strategies that would increase the randomization rate.

b. Baseline Data

Reports to the MTOPS Steering Committee will consist of comparisons between the treatment groups and clinical centers in the characteristics of the participants. If differences are found among the clinical centers, procedures at each center will be reviewed to attempt to distinguish between differences in the participant population and differences caused by variation in the participant selection or measurement techniques.

c. Case Report Form Completion

The BCC will prepare reports for the MTOPS Steering Committee presenting tabulations for the number of forms received, the number of edit messages, and the number of overdue forms and responses to edits. Missing data, particularly on outcome variables, will effectively reduce the power of analyses. In fact, systematic patterns of missing data could bias the results of the trial. Therefore, many of the procedural details outlined in the operations manual are designed to minimize the amount of missing data. The item-specific missing value rate on each CRF will be monitored throughout the full-scale clinical trial.

d. Other Reports

The BCC will prepare reports for the MTOPS Steering Committee on participant

compliance with the protocol and inactive follow-up. Other reports will be developed, as needed, based on requests from the Steering Committee and associated subcommittees.

SECTION 8

Statistical Considerations

A. Sample Size and Power

1. Sample Size Requirement

In the full-scale trial, a total number of 2,448 participants will be needed (612 per treatment group) in order to have 80 percent power to detect a one-third reduction in the time to clinical progression of BPH in an active drug group compared to the placebo group ($\alpha = 0.05$, two-sided). This figure includes a Bonferroni adjustment (Miller, 1981) to control the probability of a Type I error for three pairwise comparisons, i.e., each treatment group versus the placebo. The sample size formula used is found in Lachin and Foulkes (1986, eq. 6.2), which assumes an exponential cumulative incidence distribution with a 25 percent incidence over five years (i.e., hazard rate in the placebo group of 5.8 percent per year). Also assumed is that the randomization period will last 2 years and there will be 4 to 6 years of follow-up per participant.

Long-term clinical trials clearly demonstrating the probability of disease progression over time are lacking. A study by Craigen et al. (1969) suggests that 50 percent of participants will have progression of disease necessitating active treatment within a five year time frame. This study may overestimate the true probability of progression, since this group of participants had severe symptoms at entry. The Veterans Administration Cooperative Trial of watchful waiting versus surgery, as yet unpublished, demonstrated an overall failure rate of 18 percent in the watchful waiting group over three years. Using these two figures as a range, the rate of progression of 25 percent over 5 years in this protocol was obtained.

Information received from the Olmsted County BPH Trial (personal communication, Michael M. Lieber, M.D.) indicated that 13.5 percent of the cohort of men between 50 and 80 with an initial AUA symptom score of 8 or more and an initial flow rate of 15 mL or less had an increase of 4 or more in their AUA symptom score within 3.5 years of follow-up; this equates to an exponential cumulative incidence over five years of 19 percent. The Veterans Administration study and, α-blocker and finasteride studies have demonstrated a one percent probability of retention per year in participants managed on placebo and watchful waiting. Likewise, the probability of the development of renal insufficiency, recurrent urinary tract infections and urosepsis Pis estimated to be approximately one percent per year.

a. Adjustment for Losses to Follow-up

In any clinical trial, losses to follow-up are inevitable. One should build the losses to follow-up into the sample size calculation to ensure that power will not be reduced substantially (Lachin and Foulkes, 1986). Assuming an exponential loss to

follow-up hazard rate of 5 percent per year, one would adjust the necessary sample size to 2,752 (688 per treatment group). Because we are interested in detecting a 33 percent difference in a "real world" setting, rather than a 33 percent pharmacologic difference, no adjustment for treatment non-compliance will be made. Therefore, the total sample size goal for the full-scale trial is 2,800 participants (700 per treatment group.

2. Factors Affecting Study Power

The power of the study can be affected if the sample size differs from the goal of 2,800. For example, if all other parameters are kept constant, but the attained total sample size is only 2,400 (600 per treatment group), the power drops to 72 percent. A total sample size of 2,000 (500 per treatment group) will give 63 percent power.

While we give 25 percent as the incidence rate over a five year period in the placebo treated group, the data to support this assumption is minimal. If the actual incidence rate is less, power will be less. For example (assuming a sample size of 2800), if the incidence rate is only 20 percent over five years, power decreases to 69 percent. At the 15 percent incidence rate, power is only 54 percent. However, if the actual incidence over five years in the placebo group is 30 percent, power increases to 87 percent.

B. Interim Analysis Method

The Lan-DeMets (1983) spending function approach will be used to adjust the probability of a Type I error for testing the primary study hypothesis when interim "looks" of the data are taken by the External Advisory Board. The Lan-DeMets procedure is flexible, in that the number of looks does not have to be specified in advance, the time interval between looks does not have to be the same throughout the trial, and, if necessary, it is easy to switch from occasional to continuous monitoring of the data at any point during the trial (Lan, Rosenberger, and Lachin, 1993).

The rate at which the Type I error is spent is a function of the fraction of total information available at the time of the interim analysis (i.e., information time). For an interim analysis using the logrank test (i.e., time to BPH progression), the information time is the fraction of the total number of BPH progression events to be accrued in the entire trial. Since the total number of events to be accrued is unknown, an estimate of the information time will be used based on the fraction of total patient exposure (Lan and Lachin, 1990).

C. Statistical Analysis Plan

The principal analyses of primary and secondary endpoints will employ the "intent-to-treat" approach (Peduzzi, Wittes, et al., 1993). The intent-to-treat analyses will include all randomized patients. All statistical tests will be two-sided. The overall

significance level of the primary endpoint will be $\alpha = 0.05$. However, because interim analyses will be conducted throughout the trial, the significance levels used in the interim and final analyses of the primary endpoint will be adjusted to account for the multiplicity of interim analyses.

Baseline Characteristics. Analysis of homogeneity of baseline characteristics among the four treatment groups will be carried out using standard nonparametric statistical techniques, such as Fisher's exact test for categorical data (Agresti, 1990), and the Kruskal-Wallis test for ordinal or continuous data (Conover, 1980).

Primary Endpoint. Survival analysis techniques (Miller, 1981) such as the Kaplan-Meier survival estimates, the logrank test, and the Cox proportional hazards model to adjust for baseline or time-dependent covariates will be used to compare the treatment groups with respect to time to clinical progression of BPH. It should be noted that under the urn randomization scheme, the usual logrank variance is overestimated, so the logrank test will be more conservative. This is especially true if time trends are present in the data. For this reason, the correct permutational variance can be used in lieu of the logrank variance (Wei and Lachin, 1988). For the primary endpoint analysis, participants will be considered "administratively censored" if they complete the full duration of the trial without clinical progression of their BPH. Participants who prematurely discontinue their follow-up visits prior to documented clinical progression of their BPH will be "censored" as of their last follow-up visit.

Crossover to known invasive therapy prior to clinical progression of BPH may be considered a competing risk event (Lagakos, Lim and Robins, 1990). To account for crossover to known invasive therapy as a competing risk event, the treatment groups will be compared on the composite event defined as clinical progression of BPH or crossover to known invasive therapy, whichever occurs first, using the same methods described above for the primary endpoint.

Secondary Endpoints. Longitudinal data analysis techniques will be used to analyze repeated measures data (e.g., AUA symptom score, MOS-36 Health Survey score and maximal uroflow). Data will be compared across treatment groups using the nonparametric procedures of Wei and Lachin (1984) for two-group comparisons. The parametric linear random effects model of Laird and Ware (1982) can also be used to compare participant slopes over time under a linearity and normality assumption. For non-normal variates, techniques developed by Liang and Zeger (1986) can be used to compare participant slopes under a generalized linear models framework.

SECTION 9

Study Administration

A. Organization and Funding

MTOPS is being conducted by a cooperative effort among the NIDDK, the clinical centers, a diagnostic center, and a biostatistical coordinating center. The mechanism of funding is a cooperative agreement from NIDDK.

1. Participating Centers

a. Clinical Centers

There are 17 clinical centers participating in the cooperative agreement. The Principal Investigators representing the clinics have agreed to abide by study protocols and, in addition, to have comparable staff, facilities, and equipment.

b. Diagnostic Center

The Diagnostic Center (DxC) will be the central repository for tissue and serum samples collected during the trial. The DxC will serve as the central laboratory for MTOPS, and will be responsible for collection and analyses of specimens listed in Appendix E. They will serve as the monitor of quality control to ensure uniform performance of the biopsy substudy procedures among the clinical centers.

c. Biostatistical Coordinating Center

The Biostatistical Coordinating Center (BCC) is responsible for all aspects of biostatistical design, analysis, and data processing of the clinical trial. In collaboration with the Steering Committee, the BCC is responsible for document processing of the protocol and manual of operations and data collection forms development and testing. The BCC monitors protocol performance, and conducts the interim and final statistical analyses. The BCC collaborates with Steering Committee members in the preparation of publications based on the study results.

B. Committees

1. Steering Committee

The Steering Committee is the policy and decision making group, and will oversee the administrative aspects of the trial. The Steering Committee is comprised of

a Principal Investigator from each of the clinical centers, the Principal Investigators of the BCC and Diagnostic Center, and the NIDDK Project Officer. A chairperson is named in a non-voting capacity. Each of the Steering Committee members has a named alternate. The Steering Committee has primary responsibility for development and conduct of the study protocol and manual of operations (including implementation and monitoring).

2. Executive Committee

Although the Steering Committee is the decision and policy making group of the trial, a smaller group has been appointed to direct the day-to-day activities. This committee includes the Chair of the Steering Committee, the NIDDK Project Officer and the Principal Investigators of the BCC and DxC. The committee will meet by telephone conference, as necessary.

3. External Advisory Board

An External Advisory Board, a group of individuals not affiliated with any of the institutions in the cooperative agreement, is established by the NIDDK. The Board will serve as external reviewers and advisors to the NIDDK and the Steering Committee. This Board is charged with reviewing the protocol with respect to ethical and safety standards. Its principal responsibility will be to monitor the emerging results of the full-scale trial to assess treatment effectiveness, or ineffectiveness, and participant safety. The Chair of the Steering Committee, the NIDDK Project Officer and the staff of the BCC are ex-officio members of the Board.

4. Subcommittees

Subcommittees of the Steering Committee are appointed to assume specific responsibilities to help guarantee the successful implementation, monitoring and administration of the trial. Appointed subcommittees include the following: Clinical Review Subcommittee, Recruitment and Retention Subcommittee, Prostate Biopsy and PSA Subcommittee, Publications and Ancillary Study Subcommittee and Trial Coordinators Subcommittee. These subcommittees will consist of members of the MTOPS study group. Their roles and responsibilities are detailed in the Manual of Operations.

SECTION 10

Study Timetable

The outline below summarizes the timeline for the NIH-BPH pilot study and MTOPS full-scale trial:

PILOT STUDY:

Development Phase	01OCT1992 to 30NOV1993	(14 months)
Randomization Phase	01DEC1993 to 30NOV1994	(12 months)
Follow-up Phase	01DEC1993 to 31JAN1995	(14 months)
Close-out/Analysis Phase	01FEB1995 to 31MAR1995	(2 months)

FULL-SCALE TRIAL:

Transition Phase	01APR1995 to 30NOV1995	(8 months)
Randomization Phase	01DEC1995 to 30NOV1997	(2 years)
Follow-up Phase	01DEC1995 to 30NOV2001	(6 years)
Close-out/Analysis Phase	01DEC2001 to 31MAR2002	(4 months)

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