



MANUAL OF OPERATIONS

FOR

**A CLINICAL TRIAL OF MEDICAL THERAPY
OF
PROSTATIC SYMPTOMS
(MTOPS)**

SPONSORED BY

**THE NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE
AND KIDNEY DISEASES
THE NATIONAL INSTITUTES OF HEALTH**

Third Edition: October 24, 1996

Update: June 10, 1997

Update: January 1, 1999

Update: February 20, 2001

PREFACE

Editions of the Manual of Operations

The Manual of Operations for Medical Therapy of Prostatic Symptoms (MTOPS) sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK-NIH), will be maintained by the Biostatistical Coordinating Center (BCC), which is The George Washington University Biostatistics Center. Over the course of the trial, there will be new releases of the Manual of Operations or issuance of supplemental manual memoranda. Comments or questions regarding aspects of this manual, including distribution, should be directed to the staff of the BCC at the address listed in the Directory of Participants.

First Edition

The first edition of the Manual of Operations (dated July 12, 1995) was based on the pilot study manual 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 (February 28, 1996)

The release of the second edition of the Manual of Operations (dated February 28, 1996) followed modifications to the protocol, by the members of the Steering Committee. The second edition includes the following major changes to the first edition:

I. *Baseline Prostate Volumes*

Due to modifications that were made to the second edition of the protocol (dated October 23, 1995), baseline prostate volumes will be monitored. Consequently, the following changes to Form P01 (TRUS and Biopsy Information) have been made:

- A. The randomization criteria has been modified to include a baseline TRUS.
- B. The type of TRUS transducer used will be documented on Form P01.
- C. The volume will be recorded as read by the machine, irrespective of the machine used.

II. *Dispensing Coded Medications*

The following clarifications were made:

- A. Patients who decrease their dosage from 8 mg to 4 mg will not be re-challenged with the 8 mg dose.
- B. The patient must be maintained for at least seven days on the final tolerated dose before the maintenance phase medication is dispensed.
- C. The number at the bottom of the blister packs refer to lot numbers, not patient numbers.
- D. In the Doxazosin Compliance section on various forms, the dose of doxazosin question refers to dose currently being taken.
- E. Compliance Section on various case report forms
 - 1. Due to modifications in both the software and the case report forms, the compliance section was modified. There are 4 spaces to record compliance. This allows for compliance up to 9999% OR a negative compliance (3 digits with the negative sign).
 - 2. If no tablets are returned, then the number of tablets returned should be recorded as 0.

- III. *Modifications to the Diagnostic Center Section* (Chapter 8), including the fact that now shipping charges are to be billed to the Diagnostic Center's FedEx account.
- IV. The listed acceptable substitutions of Zantac and Pepcid in the Exclusionary medications section (Chapter 6, page 3), were removed because they are unacceptable substitutions.
- V. Extended explanation of how to complete edits (Chapter 9).
- VI. Expanded the Recruitment Strategies and Retention Patients on Clinical Trials Section (Chapter 3)
- VII. Clarified that biopsy results from the local pathologist must be obtained prior to randomization.
- VIII. Modifications in Distributed Data Entry System Section (Chapter 12) including:
 - A. Randomization Procedure
 - B. Change Inits/DOB
 - C. BPH Reports
- IX. *Miscellaneous Changes*
 - A. Ogden BioServices (the Drug Distribution Center) changed its name to McKesson BioServices.
 - B. Change in terminology: 'lost to follow up' changed to 'inactive follow up'.
 - C. Clarified how to assign Screening Number.
 - D. Clarified that it is acceptable for a patient to refuse to complete Form Q02 (Sexual Function Questionnaire). Their refusal should be documented in the source document.
 - E. Expanded the description of the subcommittees in the Study Organization Section (Chapter 2).
 - F. The checklist for Preparing for Randomization (Chapter 3, page 9) was modified to reflect protocol changes.

Second Edition Update (June 26, 1996)

I. *Modifications to the Protocol*

Due to modifications made to the second edition of the protocol, the following changes were made to Form B01, Chapter 11, page 3:

- A. Criteria D.6 was modified to allow for the use of tagamet.

If a patient has or is taking prescription tagamet, he can be screened after a 3 month washout period. If a patient has or is taking over-the-counter tagamet on an infrequent basis, he can be randomized at the discretion of the principal investigator provided that the patient is instructed to take a substitute (such as Pepcid).
- B. Criteria D.14: Clarified that although surgery for bladder neck obstruction is an exclusion, diagnosis of bladder neck obstruction is not an exclusion.
- C. Criteria D.15: Changed the criteria regarding a cystoscopy or biopsy of the prostate from two weeks to the past one month prior to the Screening Visit 1.

II. *Screening Period*

- A. All Screening Visit 0 contacts need to be documented in several places.

- B. Clarified that if re-screening a patient, then the same screening number should be assigned in Chapter 3, page 5.
 - C. Clarified that the medication run-in phase should be 14 days but at least 7 days in Chapter 3, page 5.
- III. *Adverse Events*
- A. Prior to randomization (during screening period), only serious events need to be documented in several places.
 - B. If a serious Adverse Event occurs, a case history must be sent to the CRC through the BCC.
- IV. *Changes to Case Report Forms*
- A. On Form E04 (Adverse Event Report) in Chapter 11, page 28, Question B.1.b. was added: **COSTART description (See COSTART Term Coding Glossary).**
 - B. On Form F01(Standard Follow-Up Visit Inventory) in Chapter 11, page 35, 51, 65, the 6 month PSA was dropped. Consequently, in the new version (3) of the form, Section K was removed.
- V. *Windows Version of Software*
- A. Instructions for new method of accessing data entry forms in Chapter 12, page 5.
 - B. Changes to PC Certification in Chapter 9, page 6 with regards to the Windows version.
- VI. *Miscellaneous Issues*
- A. Local pathology reports should be forwarded to the Diagnostic Center (Chapter 8).
 - B. Claritin D was added as an exclusionary drug in Chapter 6, page 3, but Claritin can be used as a substitution.
 - C. Posters were added in Chapter 3 under Recruitment Strategies.

Third Edition (October 24, 1996)

I. *Modifications to the Protocol*

Due to modifications made to the second edition of the protocol on March 25, 1996, the following changes were made.

- A. Change of Study Name

Study name globally changed to "A Clinical Trial of Medical Therapy of Prostatic Symptoms (MTOPS)".

- B. Exclusion criteria D.5 was modified to allow for the of a topical anti-cholinergic eye drops. The section "Instructions for Completing Form B01- Eligibility and Exclusion Inventory" was modified to reflect this change in case report form. (3)

Text of addition to criteria C.5:

"If a patient was using topical anti-cholinergic eye drops for the treatment of glaucoma, then he can be screened after a 3 month washout period."

II. *Expanded the Recruitment Strategies*

Added to the list of recruitment strategies in Chapter 3, page 2, the following: mailing lists, health fairs, and

Web site advertising.

III. *Procedure for Rescreening Patients*

Added a section, "RESCREENING" (Chapter 3, page 5), to clarify the rescreening process.

IV. *Exclusionary Medications*

Made the following changes to the Exclusionary Medications section. (Chapter 6, page 3)

A. Clarified that the exclusionary medications listing in the Manual of Operations is not all inclusive.

Text of clarification:

"It is the coordinator's responsibility to make sure that all concomitant medications that a patient is taking are not exclusionary."

B. The listing was restructured to make it easier to use.

C. At the request of the Clinical Review Committee, the following medications were added as exclusionary:

1. Ornade
2. Axid (nizatidine)

D. Modified exclusion criteria to allow cimetidine after a three month washout period.

1. Zantac and Pepcid were again added as acceptable substitutions for cimetidine.

V. *Clinical Events Protocol*

A clarification was made with regard to patients who reach a primary endpoint (AUA 4 Point Rise, Creatinine Rise, Acute Urinary Retention, Recurrent Urinary Tract Infection Event, and Incontinence Event). (Chapter 6, page 6)

The change was made in several places to reflect that if the patient is enrolled in the biopsy substudy, then a TRUS, Biopsy, and hormones should be performed at the time that the event is declared.

VI. *Randomization Exceptions Clarification*

Added a section, "PROCEDURE FOR REQUESTING RANDOMIZATION EXCEPTIONS", to clarify the procedure to obtain a randomization exception. (Chapter 3, page 8)

VII. *Chapter 5: Medical Therapy Protocol*

A new type of packaging and a new unmasking procedure were implemented. The Medical Therapy Protocol section was changed accordingly, as follows:

A. The new packaging system is described in the "TYPES OF KITS" section. (Chapter 5, page 2)

B. Doxazosin run-in and titration medications are now packaged in bottles instead of cards, so global

changes were made throughout the chapter to account for the change.

- C. The new procedure for unmasking coded medication was implemented. The section, "CODED MEDICATION UNMASKING" was added to describe the new procedure. (Chapter 5, page 7)

Text of new unmasking procedure:

"In case of emergencies, clinical sites or others (emergency rooms, physicians' offices, participants, participants' relatives, etc.) may call the MBS emergency telephone number (See Directory of Participants) for unblinding of the treatment code. The telephone number is printed on the medication label and provided in the Directory of Participants.

Upon receiving such a call, the MBS technician shall obtain all of the required information and proceed as follows:

1. The technician will contact the Pharmacist with the required information.
2. The MBS Pharmacist will then call back the originator of the request to obtain any further information.
3. Provided that the request is reasonable, the pharmacist will unblind the patient for a specific treatment (doxazosin, finasteride, or both).
4. The MBS Pharmacist will notify the BCC about the unmasking or attempted unmasking within one business day via fax."

VIII. *Chapter 8: Diagnostic Center*

Several details of the Diagnostic Center procedures were clarified in this chapter.

- A. In the "TZ and PZ Formalin-Fixed Biopsies" section, a few changes were made with respect to the surface to which a biopsy is transferred and the patient information that is recorded. (Chapter 8, page 1)
- B. In the "TZ Frozen biopsies" section, clarifications were made with regard to preparing, packing and shipping frozen biopsies. (Chapter 8, page 1)
- C. In the "Laboratory Medicine" section, several clarifications were made with respect to drawing, labeling and packing serum specimens. (Chapter 8, page 2)

IX. *Publicity and Publications*

Several changes were made to the "Presentations and Publications" section to clarify new policies developed by the Publications and Ancillary Studies Subcommittee and its Chairman. (Chapter 10, page 4)

- A. A proposal for a presentation or publication should now be submitted to the Publications and Ancillary Study Subcommittee.
- B. Addition of a sentence to detail primary paper authorship.

Text of addition:

"The primary papers submitted for publication will be under corporate authorship as the 'MTOPS Research Group'."

- C. Changed (*italics*) title of the research group to reflect new study name.

Text of change:

"Within the title of each presentation and publication will be included the phrase: *'MTOPS Research Group'*."

- D. Change (*italics*)

Text of change:

"The chairman for the development of each *secondary* manuscript will designate the senior and co-authors."

X. *Ancillary Studies*

Two changes were made to the "ANCILLARY STUDIES" section to clarify the format for proposals for ancillary studies. (Chapter 10, page 5)

- A. Addition (*italics*) of sample size to proposal.

"5) research design (*including sample size*).

- B. Addition of inclusion of planned funding in proposal.

"and 8) planned funding (*including data analysis*)."

XI. *Chapter 11: Case Report Forms*

- A. Added the section "Ordering Supplies from the BCC" to explain how case report forms and other supplies should be ordered. (page 1)

- B. The following changes were made to the Case Report Forms and are reflected in the sections noted.

1. In the "Instructions for Completing Form B01- Eligibility and Exclusion Inventory" section, clarified the exclusion criteria (Question D.14) with respect to a patient diagnosed with Prostatic Intraepithelial Neoplasia (PIN). (page 6)

Text of clarification:

"A patient diagnosed with Prostatic Intraepithelial Neoplasia (PIN) grade I or low grade PIN is eligible for the trial. However, patients with grades II or III or high grade PIN are not eligible for the trial."

2. Due to modifications in both the software and the case report forms, the compliance sections were modified for Forms F01, F03, and F06. There are 6 spaces to record compliance. This allows for compliance up to 999999% OR a negative compliance (5 digits with the negative sign).
3. In the "Instructions for Completing Form F04-Missed Follow-up Visit Report", Question B.5 was added. (page 47)

Text of addition:

"Is the patient considered to be inactive (discontinued follow-up visits) ?"

4. In the "Instructions for Completing Form Q03-Health Survey Questionnaire", Question B.4 was added to obtain whether the questionnaire was self-administered or by interview. This question will not be entered into the microcomputer. (page 60)
5. Clarified that on any of the questionnaires (Forms Q01, Q02 and Q03), if the patient changes an answer on a question, he should be instructed to put his initials next to the question, thereby acknowledging that he made the correction.
6. In the "Instructions for Completing Form Q01-AUA Symptom Questionnaire", clarified that all questions of the AUA Symptom Score must be answered in order for the patient to be eligible for randomization. (page 58)

XII. *Chapter 12: Distributed Data Entry System*

- A. The use of TeleSwitches has been implemented in order to facilitate BCC contact with the clinic microcomputers when clinic staff is not available. A section was added to describe the installation of the device. (page 1)

Text of addition:

"Attach the phone line to the modem and TeleSwitch

Plug one end of the phone cable that came with the modem into the modem's **LINE** connector. Plug the other end of the phone cable into the right side phone jack on the TeleSwitch. Plug another phone cable into the left side phone jack of the TeleSwitch at the wall outlet."

- B. A procedure for performing a mock randomization was added to the Distributed Data Entry System. (page 14)
- C. There were some changes to the reports feature of the Distributed Data Entry System.
 1. The reports available on the clinic microcomputers were updated to the Windows format. The new format was globally incorporated into Chapter 12.
 2. A report was added to enable clinic staff to print patient labels on site. The "Form Labels for Each Participant" report is described in the Description of Each Report section. (page 21)

Third Edition Update (June 10, 1997)

I. *Format Changes*

The overall format of the Manual of Operations was changed: the font was decreased and the pages are now numbered within each chapter (i.e. Chapter 4, page 10 is numbered 4-10).

II. *Biopsy Substudy*

The number of randomized patients in the biopsy substudy was increased from twenty-five percent to approximately half of the randomized patients. Changes were made in all appropriate sections.

III. *New Case Report Forms*

Six new Case Report Forms were implemented since the Steering Committee meeting on February 19, 1997. Instructions for completing each of the following new Case Report Forms was added to Chapter 11.

- A. *Adverse Event Report* (Form E05)
- B. *Serious Adverse Event Report* (Form E06)
- C. *Non-scheduled Biopsy Information* (Form P04)
- D. *Prostatitis Questionnaire* (Form Q04)
- E. *Recruitment Source Tracking Information* (Form T02)
- F. *Patient Relocation Tracking Information* (Form T03)

IV. *Subcommittee Restructuring*

Subcommittees were restructured at the Steering Committee meeting on February 19, 1997. Appropriate changes were made (Chapter 2, page 2).

V. *Exclusionary Medications*

At the request of the Clinical Review Committee, the following changes were made to the *Exclusionary Medications* section (Chapter 6, page 3).

- A. The following medications were added as exclusionary:
 - 1. DHEA
 - 2. Tegretol
- B. Axid (nizatidine) was removed.
- C. Zantac (Ranitidine) and Pepcid (Famotidine) were included as substitutions for cimetidine.
- D. Many generic names for medications were added.

VI. *Patient Relocation Protocol*

The Patient Relocation Protocol was added to the *Patient Management Protocols* to detail procedures to be followed if a patient relocates in the vicinity of another clinic (Chapter 6, page 19).

VII. *Rescreening Patients in the Biopsy Substudy*

A sentence was added in the rescreening section to clarify that if TRUS/Biopsy is repeated, hormones must be redrawn (Chapter 3, page 5).

VIII. *Additional Follow-up Biopsies*

It was decided at the Steering Committee meeting on February 19, 1997, that a patient due for a biopsy need not have the procedure performed if a prior follow-up biopsy was performed within the last three months. Additions were made in *Clinical Events Protocol* (Chapter 6, page 6), *Biopsy* (Chapter 7, page 9), and *Instructions for Completing Form POI* (Chapter 11, page 54).

IX. *Chapter 5: Medical Therapy Protocol*

Due to changes in McKesson's forms, the following changes were made to the *Medical Therapy Protocol* section:

- A. Clarified the Instructions for Completing an Agent Request Form (Page 1).
- B. Clarified that the Retitration Kit supply will be automatically replenished by McKesson when necessary (Page 2).
- C. Changed the Instructions for Returning Study Supplies to the MBS Pharmaceutical Repository.
 - 1. "Strength and Dosage Form" column changed to "Full/Partial" on Agent Return Form (Page 5).
 - 2. "Patient number" column changed to include Patient Range on the Agent Return Form (Page 5).

X. *Chapter 6: Patient Management Protocols*

At the Steering Committee meeting on February 19, 1997, several decisions were made regarding patient management. The following changes were made:

- A. "Guidelines for Coded Medication Discontinuation" section was added to the *Clinical Events Protocol* (Page 6).
- B. "Abbreviated Follow-up for Prostate and Bladder Cancer" section was added to the *Clinical Events Protocol* (Page 13).
- C. Sections were added to include Prostate and Bladder Cancer in the *Description of Clinical Events* (Page 8) and *Outline of Clinical Event Procedures* (Page 11).

XI. *Chapter 8: Diagnostic Center*

- A. Changed text in TZ Frozen biopsies (italics):

"It is very important to carry out this portion of the protocol immediately to avoid deterioration of the specimen." (Page 1)

- B. Text was added in *Laboratory Medicine* to clarify who sends the PSA results to the clinics:

"For screening visits, the results will be faxed to the clinic by the Diagnostic Center. For any follow-up PSA results, the BCC will fax the report to the clinic. For patients taking coded finasteride, this report will include a PSA value that is determined by the masking algorithm described in the protocol. Only the BCC should be contacted to obtain follow-up PSA results." (Page 2)

XII. *Chapter 9: Biostatistical Coordinating Center*

- A. The following changes were made in the *Centralized Database Management System*:

1. A change was made in the Editing Procedures section.

Text of change (italics):

"Only corrected edit reports *with permanently missing or invalid items* need to be faxed to the BCC." (Page 3)

2. An addition was made in the *Verifying a Permanently Missing or Invalid Field* section.

Text of addition:

"A brief description should be included on the edit explaining why the information is permanently missing or invalid. Please note that whenever a value is coded as permanently missing/invalid on an edit and the value is obtained at a later date, the BCC should be notified" (Page 3)

- B. "Theme Auditing Procedures" section was added to *Centralized Database Management System* section. (Page 3)

- C. Addition of a sentence in the *Data Entry Certification* section for staff who do not work on the study any longer:

Text of addition:

"If a person is no longer working on the study, the BCC must be notified." (Page 5)

XIII. *Chapter 11: Case Report Forms*

- A. The Concomitant Medication Dictionary was referred to for the proper recording of names of concomitant medications. Additions were made in all appropriate sections.

- B. It was clarified that a patient "currently taking coded medication", is a patient who took coded medication the evening before a visit. Appropriate sections were changed.

- C. The *Instructions for Completing Form F03 - Interim Visit Checklist* section was modified as follows:

1. A clarification was made as to proper usage of the case report form when a patient is not seen in the clinic (Page 42).

Text of clarification:

“This form should be completed at any visit that is not a scheduled follow-up visit. Additionally, this form should be completed if medications are mailed to the patient. This is the only situation for which the form is completed when the patient does not attend a clinic visit.”

2. Addition of text to clarify the reason for form completion when a patient comes in for a biopsy (Page 42).

Text of addition:

“Please note that if a biopsy being performed is the reason for the interim visit, the reason for interim visit is the reason why the patient was having the biopsy.”

3. Intercurrent Illness was defined as “any event that is not related to the coded medications or progression of BPH that requires the discontinuation of coded medications”.

XIV. *Chapter 12: Distributed Data Entry System*

- A. The *Data Extraction and Transmission* section was changed for clarification (Page 3).

1. Text of addition:

“The study data is transmitted to the BCC weekly. The weekly process occurs in two steps. First the data is extracted from the databases, then it is transmitted to the BCC. The following points detail information regarding the data extraction and transmission. [points were listed in previous version]”

2. The transmission process was changed and text modified accordingly.

Text removed:

“No data can be entered between extraction and transmission. Any attempt to do so will result in the message “Some transmission files have not been received by the Study Coordinating Center...” ”

- B. "STATUS DATABASE" section was added to explain the database and how to use it. (Page 22)

- C. Updated the *Reports for the BPH System*.

1. New reports include:

- a. Adverse Event Listing
- b. Birthdays
- c. Reasons for Exclusion from Randomization
- d. Recruitment Source Summary

2. Changes include:

- a. "Form labels for Each Participant" to "Randomized Patients Form Labels".

XV. *Miscellaneous*

- A. It was clarified that placebo run-in medication is not considered coded medication in all appropriate sections.
- B. A clarification was added to the *Reporting Serious Adverse Drug Experiences* section.

Text of clarification:

"If medications are discontinued without any underlying adverse event, then only a case history must be written for the CRC and sent to the BCC." (Chapter 6, page 15)

- C. The study name was changed in the second edition of the protocol dated March 25, 1996 from "NIH - BPH Clinical Trial" to "MTOPS". Some sections has not previously incorporated the new name. All appropriate changes were made.
- D. Notes on Follow-up Case Report Form Completion (Chapter 4, page 5)

Text of addition:

"Blood pressure and medication dispensing/compliance information data is collected whenever the patient is seen (titration visits, standard follow-up visits, interim visits). It is important to not duplicate this information by completing more than one of these visit case report forms whenever a patient is seen for more than one "type" of visit. The study coordinator should determine which type of visit is more significant and capture that information on the appropriate visit form. For example, if a patient has been re-challenged, and a titration visit falls within the window of a standard follow-up visit, then the Standard Follow-up Visit Inventory (Form F01) should be completed instead of the Titration Visit Inventory (Form F06).

Note: Generally, an Interim Visit Checklist (Form F03) is only completed if the patient is being seen and it does not fall within the window of the other types of visits (e.g., titration, standard, major)."

Third Edition Update (January 1, 1999)

I. *Addition of Urosepsis to the Primary Outcome Definition*

A single episode of urosepsis due to bladder outlet obstruction was added to the definition of recurrent urinary tract infections for clinical progression of BPH. Changes were made in all appropriate sections.

II. *Additional TRUS at End of Study*

It was decided at the Steering Committee on October 7, 1998 that a TRUS will be performed at the end-of-study visit on all randomized patients. Changes were made in all appropriate sections.

III. *New Case Report Forms*

Two new Case Report Forms were implemented since the Steering Committee meeting on September 23, 1997. Instructions for completing each of the following new Case Report Forms were added to Chapter 11.

Changes were made in all appropriate sections.

- A. *Missed Biopsy Report* (Form R06)
- B. *PSA Collection Report* (Form R07)

IV. *Subcommittee Restructuring*

The Medication Adherence Committee was established at the Steering Committee on January 22, 1998. The Recruitment and Adherence Committee became the Protocol Adherence Committee. The Urodynamics Subcommittee was removed. Appropriate changes were made (Chapter 2, page 1).

V. *Exclusionary Medications*

- A. Principal Investigators voted at the Steering Committee on May 20, 1997, to allow the use of selected serotonin uptake inhibitors. Changes were made to the *Exclusion Criteria* section (Chapter 3, page 3) and to the *Screening Visit 1 Inventory* (Chapter 11, page 8).

Text of addition (italics):

"The patient has taken phenylephrine, pseudoephedrine, imipramine, an anticholinergic or cholinergic medication within 4 weeks of the 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 updated inhibitors anti-depressants [*Paroxetine HCl (Paxil)*, *Fluoxetine HCl (Prozac)* or *Sertraline HCl (Zoloft)*]."

- B. New exclusionary medications were noted at the Steering Committee on January 22, 1998. The following medications were added to the *Exclusionary Medications* section (Chapter 6, page 3).
 - 1. Propecia (Finasteride, Proscar)
 - 2. Flomax (Tamsulosin)

VI. *Dispensing Medications*

It was decided at the Steering Committee on October 7, 1998, that if a patient misses or is going to miss a quarterly visit, one kit of study medications can be mailed or dispensed ahead of time. It is not acceptable to do so for a second missed visit. A sentence was added to *Dispensing Guidelines* step 7 (Chapter 5, page 3) and to the *Instructions for completing the Interim Visit Checklist* (Chapter 11, page 42).

Text of addition:

"(Note: It is acceptable to dispense coded medications in advance or mail coded medications for one missed follow-up visit. It is unacceptable to do so for two or more consecutive missed visits.)"

VII. *Chapter 4: Follow-up Protocol*

Two sections were added:

- A. "ADVERSE EVENT REPORTING" section was added to define consistent methods of reporting adverse events (Page 14).
- B. "FREE PSA TESTING" section was added to define steps involved in collecting a free PSA (Page

4).

VIII. *Chapter 5: Medical Therapy Protocol*

- A. It was decided at the Steering Committee on September 23, 1997, to allow titration of doxazosin up to 8mg after back-titrating to 4mg in the investigator feels it is appropriate. A sentence was added to the *Special Notes on Dispensing Doxazosin* section (Page 3).

Text of addition (italics):

"Participants who decrease their dosage of doxazosin from 8mg to 4mg *may be rechallenged with the 8mg dose at the discretion of the principal investigator.*"

- B. Clarifications were made in the *Coded Medication Unmasking* section (Page 7).

IX. *Chapter 6: Patient Management Protocols*

Several changes were made to the *Clinical Events Protocol* (Page 6).

- A. A clarification was made to the AUA 4 Point Rise Clinical Event description to take into consideration a decision made at the Steering Committee meeting on May 6, 1998.

Text of clarification:

"By protocol, declaration of the event is subject to a confirming symptom score in 2 to 4 weeks from the initial rise. However, an event can be declared if the confirming visit is performed within the window of the next quarterly visit."

- B. A description of "Clinical Event: Crossover to Open-Label Medication" was added to the *Clinical Events Protocol*.
- C. Text was removed from the "Clinical Event: Inactive Follow-up" section that stated a patient could not brought back into the study if he had been inactive for greater than one year.
- D. Layout changes were made to the *Outline of Clinical Event Procedures*. "Update Status Database" was added to each clinical event.
- E. The definition of a Serious Adverse Event was modified to include "Treatment to prevent a serious event" in the *Reporting Serious Adverse Drug Experiences* (Page 15).
- F. Addition of section "Letters to the Record and Clinical Review Committee (CRC) Reports" which outlines information required in such letters to the record (Page 13).

X. *Chapter 8: Diagnostic Center*

- A. "Instructions for collecting a Free and Total PSA" was added (Page 3).
- B. Minor changes were made throughout this chapter.

XI. *Chapter 10: Policies*

"Review of Presentations" policy was added to the *Publicity and Publication* section (Page 3).

XII. *Chapter 11: Case Report Forms*

Several minor modifications and additions were made to this chapter.

- A. Instructions for deleting a Case Report Form were added to the *General Instructions* (Page 1).

Text of addition:

"If a Case Report Form is deleted, a big red 'X' should be drawn on the first page and a short description should include the reason why the Case Report Form was deleted. Coordinator should initial and date the deletion."

- B. Mandatory use of patient labels on all follow-up forms was added to the *Instructions for Completing the Patient Identification* (Page 1).

- C. Text was added to the *Major Follow-up Visit Inventory Instructions* to clarify order of procedures for biopsy substudy patients (Page 39).

Text of addition:

"If a patient is in the biopsy substudy, all procedures and questionnaires must be completed before the biopsy is performed."

- D. Clarified text in the *Interim Visit Checklist* section (Page 42).

1. If the patient is dropping off or picking up his coded medication, 'Dispense more Medication' should be checked as the reason for the visit.
2. If the patient is picking up medication for an intercurrent illness (e.g., caverjet, viagra, muse, etc.), 'Intercurrent Illness Event' should be checked as the reason for the visit.

- E. *Missed Follow-up Visit Report* instructions were modified.

1. Clarified that the form should be completed for any missed visit, regardless of whether or not the patient is on abbreviated protocol.
2. Additional text was added to clarify when the form should be completed (Page 47).

Text of addition:

"If the clinic is notified ahead of time that the visit will be missed (including that the patient will be inactive or had died), a Form F04 must be completed for the first missed visit."

- F. Addition to the *Instructions for Completing TRUS and Biopsy Information* section to clarify follow-up biopsy procedure for substudy patients (Page 54).

Text of addition:

"All biopsies performed for patients in the biopsy substudy should be performed using study

protocol with tissue sent through the Diagnostic Center."

- G. Addition to the *Instructions for Completing Non-Scheduled Biopsy Information* section to clarify biopsy procedure for patients who are not participating in the substudy (Page 56):

Text of addition:

"Note: If a patient did not sign a informed consent to be in the biopsy substudy and thus did not have a biopsy at baseline, follow-up biopsies for this patient should not be performed using study protocol with tissue sent to the Diagnostic Center. If a patient who is not in the biopsy substudy requires a biopsy after randomization, the biopsy should be performed outside of the study and this form should be completed."

- H. *AUA Symptom Questionnaire* section was modified to clarify that if a patient indicates more than one answer for a question or misses answers, the symptom score cannot be tabulated (Page 58).

XIII. *Chapter 12: Distributed Data Entry System*

- A. The TeleSwitch instructions were updated in the instructions for *Microcomputer Set-up* (Page 1).
- B. Step 1, "Exit Windows", was added to the steps for Rebooting the Computer listed in the *Communication* section (Page 2).
- C. The following features were added to the *MTOPS System Group* (Page 4):
 - 1. MTOPS Theme Audits
 - 2. All files on Drive C Tape Backup
 - 3. Status Database Data Entry
 - 4. Print Status Database
 - 5. Elapsed Days
 - 6. Clinic Staff Database
- D. "DATA BACKUPS" section was added to explain data backups and how to execute them (Page 5).
- E. Deleting and Exiting a Case Report Form instructions were added to the *MTOPS Data Entry Case Report Form Entry Software* section (Page 8).
- F. "FOLLOW-UP PSA AND AUA REPORTS" section was added to explain the two follow-up reports sent to clinics after data transmission each week (Page 15).
- G. *The Reports for the BPH System* section was updated as follows (Page 16).
 - 1. New reports include:
 - a. Inactive Patients Report to Liaison
 - b. Patients not seen in > 150 days Report to the Liaison
 - c. Post-randomization Forms with Discrepant Visit Date/Week
 - d. Schedule of Follow-up Visits - Calendar
 - e. Schedule of Follow-up Visits - Listing
 - 2. Additions include:
 - a. "Flagged AUA Scores Without E01 Report" indicates if the patient has crossed

- b. over to invasive therapy.
 - b. “Patients in Biopsy Substudy Report” reports a one year biopsy was done if it was performed within the window of 3 months prior to and 6 months post the one year target date.
 - c. “Quarterly Missed Visits Report” indicates whether the patient was classified as inactive on the Missed Visit Report.
- H. A section to describe "THEME AUDITS" was added (Page 21).
- I. “STATUS DATABASE” section was modified to include the status for patients on abbreviated protocol (Page 22).
- J. "CLINIC STAFF DATABASE" section was added to explain the database and how to use it (Page 22).

Third Edition Update (February 20, 2001)

I. *Addition of End of Study Procedures*

The Steering Committee voted by ballot to add the following End-of-Study procedures to the MTOPS protocol (third edition update dated, October 13, 2000). These changes were added to the Manual.

- A. For patients in the biopsy substudy, End of Study transrectal ultrasound and biopsy will be performed either at the 5-year follow-up visit or at the last follow-up visit, whichever occurs first. For patients not in the biopsy 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.

The “BIOPSY” section of the Manual was modified to incorporate this change (Chapter 7, Page 9).

Text of modification (*italics*):

“Each patient will undergo three biopsy procedures: after Screening Visit 2, at the 12-Month Visit, and *either at the 5 year follow-up visit or at the last follow-up visit, whichever occurs first.*”

- B. Coded medications will be offered post End of Study until the disclosure of the final study results and treatment code assignments. The “END-OF-STUDY VISIT SCHEDULE AND PROCEDURES” section was modified to incorporate this addition (Chapter 4, Page 5).

Text of addition:

“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.”

“Participants who elect to receive coded medications at the last follow-up visit will be assessed for adverse events every 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.

The following forms will be completed:

- F07 - Post End-of-Study Visit Inventory
- E05 - Adverse Event Report (if necessary)
- E06 - Serious Adverse Event Report (if necessary)

The following procedure will be performed:

- Vital signs (if not Separation Visit)
- Counting returned coded medications
- Dispensing coded medications
- Assessment of Adverse Events”

The Steering Committee agreed on the following modifications to End of Study procedures:

- C. Procedures to be performed at the end of study visit were clarified (Chapter 4, Page 5).

Text of clarification:

“Whenever a patient reaches the end of the study whether it be for an event, or simply completion of the study, the following forms should be completed:

- F01 - Standard Follow-up Visit Inventory
- Q01 - AUA Symptom Questionnaire
- E05 - Adverse Event Report (if necessary)
- E06 - Serious Adverse Event Report (if necessary)

If the patient did not have a major visit within the window June 1, 2001 through August 31, 2001, the following forms will also be completed:

- F02 - Major Follow-up Visit Inventory
- Q02 - Sexual Function Questionnaire
- Q03 - Health Survey Questionnaire
- Q04 - Prostatitis Questionnaire
- R07 - PSA Collection Report”

- D. A section was added, “SUMMARY OF END-OF-STUDY CASE REPORT FORMS”, to list the new case report forms that will be utilized at the end-of-study and at post end-of-study visits (Chapter 4, Page 5).

Text of addition:

“Post End-of-Study Visit Inventory (Form F07)

This form should be completed at any visit that takes place after the end-of-study visit. Separation visits will be scheduled for all patients who attend an end-of-study visit whether or not they are continuing on coded medications.

Final Status Report for Inactive Patients (Form R10)

This form is completed for all patients who are inactive prior to death or the administrative censoring date of November 30, 2001. The purpose of this form is to document the final status of

the aforementioned patients as of November 30, 2001.”

II. *New Case Report Forms*

The Executive Committee voted to implement four new case report forms. Instructions for completing each of the following new case report forms were added to Chapter 11. Changes were made in all appropriate sections.

The four new case report forms are:

- ! Post End-of-Study Visit Inventory (Form F07)
- ! Prostate Cancer Registry Report (Form R08)
- ! Prior Use of Viagra Report (Form R09)
- ! Final Status Report for Inactive Patients (Form R10)

III. *Changes to Case Report Forms*

- A. A question regarding Viagra usage was added to the following case report forms: F01, F03, F06 and P01.

Text of addition:

“Has the patient taken viagra (sildenafil citrate) since the last visit?

Record YES if the patient has taken viagra since his last scheduled or interim visit.”

- B. Two additional reasons for an interim visit were added to the Interim Visit Checklist (Chapter 11, Page 42).

Text of addition:

“C.10 TRUS and biopsy

Record an 'X' in the corresponding box if the interim visit is scheduled for the purpose of performing a TRUS with or without biopsy.
Also complete part III of this form ONLY.

C.11 Blood draw (other than creatinine rise)

Record an 'X' in the corresponding box if the interim visit is scheduled for the purpose of drawing blood for reasons other than for a creatinine rise.
Also complete part III of this form ONLY.”

- C. The Non-scheduled Biopsy Information CRF (Form P04) was clarified to include invasive therapy procedures that entail pathology reports for prostate tissue taken. A new question and skip pattern was added (Chapter 11, Page 56).

Text of addition:

“B.3 Is the pathology information from a TRUS/biopsy (not an invasive therapy)?

Record YES if the pathology information is from a TRUS/biopsy.

If YES, continue. If NO, SKIP to question C.2.”

- D. Standard Follow-up and Titration Visits were added as options for type of visit on the PSA Collection Report (Form R07) (Chapter 11, Page 64).
- E. Patient’s electronic email address was added to the Patient Tracking Information CRC (Form T01) (Chapter 11, Page 69).

Text of addition:

“A.9 Patient’s electronic email address if applicable.

Record the patient’s email address if he has one.”

IV. *Drug Distribution Center*

The study drug distribution center changed its name from “McKesson Bioservices” to “McKessonHBOC Clinical and Biological Services”. This change was made throughout the manual.

V. *Chapter 3: Pre-randomization Activities*

Added Form T02 (Patient Tracking Information) to the list of required case report forms completed for each screening attempt (Page 5).

VI. *Chapter 4: Follow-up and End-of-Study Protocol*

- A. Several sections were modified and added for end-of-study procedures (see *Addition of End of Study Procedures*)
- B. The “ADVERSE EVENT REPORTING” section was moved to chapter 6.
- C. The “PSA TESTING” section was moved to chapter 7.

VII. *Chapter 6: Patient Management Protocols*

- A. A clarification was made with regard to the definition of orthostatic hypotension (Page 2).

Text of clarification (*italics*):

“For the purposes of this study, orthostatic hypotension will be defined as a decrease of *greater than 20 mmHg* in supine to standing systolic blood pressure, a decrease of *greater than 10 mmHg* in supine to standing diastolic blood pressure or the development of significant postural hypotension.”

- B. Added text to the exclusionary medication section to clarify that if the patient elects to take an exclusionary medication, a case history must be sent to the BCC (Page 3).

Text of addition:

“If the patient elects to take an exclusionary medication, a case history must be sent to the BCC.”

- C. The Guidelines for Coded Medication Discontinuation were updated by the Medication Adherence Committee (Page 6).
- D. The Guidelines for Coded Medication Rechallenge were added to the “CLINICAL EVENTS PROTOCOL” section (Page 7).
- E. A clarification was made to declaration of a Creatinine Rise Event (Page 8).

Text of clarification (*italics*):

“Declaration of the event is subject to a confirming serum creatinine result within 4 weeks from the initial rise *and confirmation by the CRC.*”

- F. A clarification was made to patients diagnosed with bladder cancer. A diagnosis of bladder cancer is treated the same as prostate cancer, in that, the patient may continue coded medications at the PI’s discretion until the patient crosses-over to known invasive therapy (Page 8).

Text of clarification (*italics*):

“Clinical Event: Prostate / Bladder Cancer

Diagnosis of prostate *or bladder cancer* should be recorded on the Adverse Event Report (Form E05) and Serious Adverse Event Report (Form E06). Until a patient has crossed-over to known invasive therapy, the patient can continue on coded medication at the Principal Investigator’s discretion and continue follow-up visits. If a patient has crossed-over to known invasive therapy, coded medications must be discontinued and follow-up visits are continued on the appropriate abbreviated protocol (see Abbreviated Follow-up for Prostate *and Bladder Cancer* in Chapter 6, page 13).”

- G. A clarification was made to treatment non-compliance patients (Page 8).

Text of addition:

“Treatment non-compliers have the option to rechallenge coded medications unless there is less than 6 months until their End-of-Study visit target date.”

- H. A clarification was made to patients on abbreviated protocol (Page 13).

Text of clarification:

“For patient receiving known *invasive* therapy for their prostate or bladder-sparing procedure for their bladder cancer, a simplified follow-up protocol will be initiated.”

- I. A new section was added, “PATIENT ADHERENCE”, which includes the section “Retaining Patients on Clinical Trials” from chapter three, a new section listing the “Protocol Adherence Guidelines” and the previously listed section titled “Patient Relocation Procedures” (Page 16).

VIII. *Chapter 8: Diagnostic Center*

- A. Clarified that Free and Total PSA should be collected after results are obtained from the annual

visit (Page 2).

Text of clarification (*italics*):

“A Principal Investigator may request a special free and total PSA test. *This special test is in addition to the serum for PSA and archive which is collected at an annual visit, and should be collected after results are obtained from the annual visit.*”

- B. Several clarifications were added to the Shipping Instructions section (Page 3).

Text of clarification (*italics*):

“The Diagnostic Center provides a *FedEx account number for billing purposes*. Please call the Diagnostic Center for this information. *Clinics should contact their local FedEx office for shipping labels, shipping bags and dry ice labels.*”

- C. Some notes were added to step 2 in the “FROZEN SAMPLE TRANSPORTATION” section (Page 4).

Text of addition (*italics*):

“2. Specimens should be sent....*Please check with the Diagnostic Center for their holiday schedule. Do not select Saturday delivery.*”

IX. *Chapter 9: Biostatistical Coordinating Center*

Remote Data Management System configuration was updated with current hardware components of the microcomputer workstation (Page 1).

Text of modification:

“Dell Pentium III
550 megahertz with 128 mbram
Windows 98
hp Laserjet 1100 xi printer
internal tape backup
external 56k modem”

X. *Chapter 10: Policies*

The address for grant questions was updated (Page 1).

Text of modification:

“NIH/NIDDK/DKUHD
6707 Democracy Blvd., Room 617
Bethesda, MD 20892”

XI. Chapter 11: Case Report Forms

- A. Clarified notes on ordering supplies from the BCC (Page 1).

Text of clarification:

“Additional year packets are sent periodically for active patients randomized. If a packet is needed for an inactive patient who has reactivated, the patient number should be included on the order form.”

- B. Clarified that a T02 must be completed for every screening B01 and B02 completed.
- C. A “patient currently taking a coded medication” was clarified to the “patient having taken the medication *within 24 hours prior to the visit*”.
- D. Visits at which to complete the Prostatitis Questionnaire were clarified to Screening Visit 2, Major Follow-up Visits and End of Study (Page 60).
- E. Two clarification notes were added to the PSA Collection Report (Form R07) (Page 64).

Text of clarification:

“Note: For a participant who has rechallenged coded finasteride within the last 3 months, PSA draw should be postponed until 3 months have elapsed although it is not required.

Note: After this form is entered and transmitted to the BCC, questions B.4 and B.4a cannot be changed. Therefore, all information should be verified before entering the form into the clinic computer.”

XII. Chapter 12: Distributed Data Entry System

- A. The following sections were updated for the new MTOPS computers:
1. MICROCOMPUTER SET-UP
 2. COMMUNICATIONS
 3. WINDOWS FEATURES
 4. DATA BACKUPS
 5. MTOPS DATA ENTRY - MAIN MENU WINDOW
- B. According to FDA guidelines, the BCC updated the study software to include password security. A section to describe “PASSWORDS” for data entry was added (Page 2).
- C. “Resetting PCAnywhere” was added to the “COMMUNICATIONS” section (Page 2).
- D. A section to describe “Buttons on the Main Window” was added to the “MTOPS DATA ENTRY - MAIN MENU WINDOW” section (Page 5).
- E. Several reports on the clinic computers were modified in the “REPORTS FOR THE MTOPS SYSTEM” section to incorporate end-of-study procedures and other minor changes (Page 16).

New reports added to the clinic computers since the last edition include:

1. BCC Mailing Labels
2. Compliance - Dose of Doxazosin
3. Compliance - Over Time
4. Compliance - % \geq 80% Compliant @ Quarterly Visits (GRAPH)
5. Compliance - % \geq 80% Compliant @ Quarterly Visits
6. Data Entry Delay
7. Dissatisfied with Quality of Life
8. Maximum Flow Rate Over Time (TABLE)
9. Maximum Flow Rate Over Time (GRAPH)
10. Not Seen \geq 70 Days
11. PSA, DRE and TRUS Volume
12. Primary Endpoints Declared
13. Quarterly Visit Attendance
14. Visits and Medication Status Over Time

- F. A section to describe “PAC REPORTS” that were added to the software was added (Page 24).

TABLE OF CONTENTS

CHAPTER 1: OBJECTIVES AND STUDY DESIGN 1-1

 INTRODUCTION 1-1

 PRIMARY RESEARCH QUESTION 1-1

 Acute urinary retention 1-1

 Renal insufficiency due to BPH 1-1

 Recurrent urinary tract infections / urosepsis 1-1

 Incontinence 1-1

 Increase in AUA symptom score index 1-1

 SECONDARY RESEARCH QUESTIONS 1-2

 SUBGROUP HYPOTHESES 1-2

 STUDY DESIGN 1-3

 TREATMENT GROUPS 1-3

CHAPTER 2: STUDY ORGANIZATION 2-1

 ORGANIZATIONAL STRUCTURE 2-1

 PARTICIPATING CENTERS 2-1

 Clinical Centers 2-1

 Diagnostic Center 2-1

 Biostatistical Coordinating Center 2-1

 COMMITTEES 2-1

 Executive Committee 2-1

 Steering Committee 2-1

 Clinical Review Committee 2-2

 Medication Adherence Committee 2-2

 Protocol Adherence Committee 2-2

 External Advisory Board 2-2

 SUBCOMMITTEES 2-2

 Publications Subcommittee 2-2

CHAPTER 3: PRE-RANDOMIZATION ACTIVITIES 3-1

 RECRUITMENT STRATEGIES 3-1

 ELIGIBILITY CRITERIA 3-2

 EXCLUSION CRITERIA 3-3

 CONSENT 3-4

 SCREENING PERIOD 3-4

 RESCREENING 3-5

 MEDICATION RUN-IN PERIOD 3-6

 RANDOMIZATION 3-6

 SUMMARY OF PRE-RANDOMIZATION CASE REPORT FORMS 3-6

 PRE-RANDOMIZATION VISIT SCHEDULE AND PROCEDURES 3-7

 PROCEDURE FOR REQUESTING RANDOMIZATION EXCEPTIONS 3-8

 CHECKLIST FOR PREPARING FOR RANDOMIZATION 3-9

CHAPTER 4: FOLLOW-UP AND END-OF-STUDY PROTOCOL 4-1

 SUMMARY OF FOLLOW-UP CASE REPORT FORMS 4-1

 FOLLOW-UP VISIT SCHEDULE AND PROCEDURES 4-3

 Notes on Follow-up Case Report Form Completion 4-5

 SUMMARY OF END-OF-STUDY CASE REPORT FORMS 4-5

 END-OF-STUDY VISIT SCHEDULE AND PROCEDURES 4-5

Post End-of-Study Visits and the Separation Visit	4-6
CHAPTER 5: MEDICAL THERAPY PROTOCOL	5-1
ORDERING	5-1
Instructions for Completing an Agent Request Form	5-1
TYPES OF KITS	5-2
RECEIPT AND STORAGE	5-3
ACCOUNTABILITY	5-3
DISPENSING	5-3
Guidelines	5-3
Special Notes on Dispensing Doxazosin	5-4
Special Notes on Dispensing Finasteride	5-4
Dispensing Run-In Medication	5-5
Dispensing Titration Medication	5-5
Dispensing Maintenance Phase Medication	5-5
RETURNS	5-5
Instructions for Returning Study Supplies to the MBS Pharmaceutical Repository	5-6
CODED MEDICATION UNMASKING	5-7
CHAPTER 6: PATIENT MANAGEMENT PROTOCOLS	6-1
BLOOD PRESSURE MANAGEMENT PROTOCOL	6-1
Office Blood Pressure (BP) Measurement	6-1
Standardization of Technique for Accurate BP Measurement	6-1
Orthostatic Hypotension	6-2
EXCLUSIONARY MEDICATIONS	6-3
CLINICAL EVENTS PROTOCOL	6-6
Background	6-6
Guidelines For Coded Medication Discontinuation	6-6
Guidelines for Coded Medication Rechallenge	6-7
Description of Clinical Events	6-8
Summary of Significant Clinical Event Protocols	6-11
Outline of Clinical Event Procedures	6-11
Abbreviated Follow-up for Prostate and Bladder Cancer	6-13
Letters to the Record and Clinical Review Committee (CRC) Reports	6-13
ADVERSE EVENT REPORTING	6-14
Reporting Serious Adverse Drug Experiences:	6-15
PATIENT ADHERENCE	6-16
Retaining Patients on Clinical Trials	6-16
Protocol Adherence Guidelines	6-17
Patient Relocation Procedures	6-19
CHAPTER 7: PROCEDURES PROTOCOLS	7-1
UROFLOWMETRY PROCEDURE	7-1
RESIDUAL VOLUME PROCEDURE	7-1
SERUM COLLECTION FOR SERUM PSA AND HORMONES	7-3
FREE PSA TESTING	7-4
URINALYSIS PROTOCOL	7-4
SERUM COLLECTION FOR HEMATOLOGY AND CHEMISTRIES	7-4
Hematology Profile	7-5
Chemistry Profile	7-5
TRANSRECTAL ULTRASOUND OF THE PROSTATE	7-6

BIOPSY	7-9
CHAPTER 8: DIAGNOSTIC CENTER	8-1
ANATOMIC PATHOLOGY (Tissue Biopsies)	8-1
General Considerations	8-1
TZ and PZ formalin-fixed biopsies	8-1
TZ Frozen biopsies	8-1
Pathology Reports	8-2
LABORATORY MEDICINE (Serum Specimens)	8-2
SHIPPING INSTRUCTIONS	8-3
FORMALIN FIXED TISSUE TRANSPORTATION	8-4
FROZEN SAMPLE TRANSPORTATION	8-4
Centrifugation Note	8-4
CHAPTER 9: BIOSTATISTICAL COORDINATING CENTER	9-1
REMOTE DATA MANAGEMENT SYSTEM	9-1
Clinical Centers	9-1
Specific Tasks	9-1
System Support	9-2
Configuration	9-2
Security	9-2
Diagnostic Center	9-2
CENTRALIZED DATABASE MANAGEMENT SYSTEM	9-3
Editing Procedures	9-3
Specific Notes for Completing Edit Reports	9-3
Verifying a Permanently Missing or Invalid Field	9-5
Responding to a Temporarily Missing or Invalid Field Edit	9-5
Theme Auditing Procedures	9-5
PERFORMANCE MONITORING	9-5
Training Workshop	9-5
Clinical Coordinator Certification	9-6
Provisional Certification	9-6
Full Certification	9-6
Data Entry Certification	9-6
Data Audit Visits	9-7
Clinical Monitoring Visits	9-7
Performance Reports	9-8
BIOSTATISTICAL CONSIDERATIONS	9-8
Intention-to-Treat	9-8
Randomization Scheme	9-9
Sample Size and Power	9-9
Analytic Methods	9-10
Interim Analyses	9-11
Procedures for Monitoring Baseline Prostate Volumes	9-13
CHAPTER 10: POLICIES	10-1
PROTOCOL INTERPRETATION DURING THE TRIAL	10-1
INFORMED CONSENT	10-1
SHIPMENT OF DRUG SUPPLIES	10-2
PROTOCOL CHANGES DURING THE TRIAL	10-2
Background	10-2

Policy	10-2
Procedures	10-3
PUBLICITY AND PUBLICATIONS	10-3
Press Releases and Interviews	10-4
Presentations and Publications	10-4
Review of Publications	10-4
Review of Presentations	10-5
ANCILLARY STUDIES	10-5
RECRUITMENT	10-5
REPORTS AND INTERIM STATISTICAL ANALYSES	10-6
Recruitment	10-6
Clinic Performance	10-6
Quality Control	10-6
Patient Safety Monitoring	10-6
CLASSIFICATION OF OUTCOME EVENTS	10-7
Clinical Events	10-7
Non-Compliant	10-7
Inactive Follow-up	10-7
CHAPTER 11: CASE REPORT FORMS	11-1
GENERAL INSTRUCTIONS	11-1
Ordering Supplies from the BCC	11-1
Procedure for Ordering Forms	11-1
Other Notes on Ordering Supplies	11-1
Instructions for Completing Patient Identification - Section A	11-1
Instructions for Completing Conclusion Box	11-2
Instructions for Completing the Information at the Top of Each Page	11-2
INSTRUCTIONS FOR COMPLETING FORM B01 - ELIGIBILITY AND EXCLUSION INVENTORY	11-3
INSTRUCTIONS FOR COMPLETING FORM B02 - SCREENING VISIT 1 INVENTORY	11-8
INSTRUCTIONS FOR COMPLETING FORM B03 - SCREENING VISIT 2 INVENTORY	11-16
INSTRUCTIONS FOR COMPLETING FORM B04 - RANDOMIZATION INFORMATION	11-18
INSTRUCTIONS FOR COMPLETING FORM B05 - MEDICATION RUN-IN INFORMATION	11-20
INSTRUCTIONS FOR COMPLETING FORM E01 - AUA SYMPTOM SCORE EVENT REPORT	11-22
INSTRUCTIONS FOR COMPLETING FORM E02 - CREATININE RISE EVENT REPORT	11-24
INSTRUCTIONS FOR COMPLETING FORM E03 - URINARY EVENT REPORT	11-25
INSTRUCTIONS FOR COMPLETING FORM E04 - ADVERSE EVENT REPORT	11-28
INSTRUCTIONS FOR COMPLETING FORM E05 - ADVERSE EVENT REPORT	11-31
INSTRUCTIONS FOR COMPLETING FORM E06 - SERIOUS ADVERSE EVENT REPORT	11-32
INSTRUCTIONS FOR COMPLETING FORM F01 - STANDARD FOLLOW-UP VISIT INVENTORY ...	11-35
INSTRUCTIONS FOR COMPLETING FORM F02 - MAJOR FOLLOW-UP VISIT INVENTORY	11-39
INSTRUCTIONS FOR COMPLETING FORM F03 - INTERIM VISIT CHECKLIST	11-42
INSTRUCTIONS FOR COMPLETING FORM F04 - MISSED FOLLOW-UP VISIT REPORT	11-47
INSTRUCTIONS FOR COMPLETING FORM F06 - TITRATION VISIT INVENTORY	11-48
INSTRUCTIONS FOR COMPLETING FORM F07 - POST END-OF-STUDY VISIT INVENTORY	11-51
INSTRUCTIONS FOR COMPLETING FORM P01 - TRUS AND BIOPSY INFORMATION	11-54
INSTRUCTIONS FOR COMPLETING FORM P04 - NON-SCHEDULED BIOPSY INFORMATION	11-56
INSTRUCTIONS FOR COMPLETING FORM Q01 - AUA SYMPTOM QUESTIONNAIRE	11-58
INSTRUCTIONS FOR COMPLETING FORM Q02 - SEXUAL FUNCTION QUESTIONNAIRE	11-59
INSTRUCTIONS FOR COMPLETING FORM Q03 - HEALTH SURVEY QUESTIONNAIRE	11-60
INSTRUCTIONS FOR COMPLETING FORM Q04 - PROSTATITIS QUESTIONNAIRE	11-60

INSTRUCTIONS FOR COMPLETING FORM R01 - CLINICAL LABORATORY NORMAL RANGE REPORT	11-61
INSTRUCTIONS FOR COMPLETING FORM R03 - DISPENSE LABEL REPORT	11-63
INSTRUCTIONS FOR COMPLETING FORM R06 - MISSED BIOPSY REPORT	11-63
INSTRUCTIONS FOR COMPLETING FORM R07 - PSA COLLECTION REPORT	11-64
INSTRUCTIONS FOR COMPLETING FORM R08 - PROSTATE CANCER REGISTRY REPORT	11-65
INSTRUCTIONS FOR COMPLETING FORM R09 - PRIOR USE OF VIAGRA REPORT	11-66
INSTRUCTIONS FOR COMPLETING FORM R10 - FINAL STATUS REPORT FOR INACTIVE PATIENTS	11-66
INSTRUCTIONS FOR COMPLETING FORM T01 - PATIENT TRACKING INFORMATION	11-69
INSTRUCTIONS FOR COMPLETING FORM T02 - RECRUITMENT SOURCE TRACKING INFORMATION	11-71
INSTRUCTIONS FOR COMPLETING FORM T03 - PATIENT RELOCATION TRACKING INFORMATION	11-72
CHAPTER 12: DISTRIBUTED DATA ENTRY SYSTEM	12-1
MICROCOMPUTER SET-UP	12-1
PASSWORDS	12-2
COMMUNICATIONS	12-2
BCC Access to Clinic PC	12-2
Rebooting the Computer	12-3
Resetting PCAnywhere	12-3
Data Extraction and Transmission	12-3
Communicating with the BCC via the 'Chat' Feature	12-4
WINDOWS FEATURES	12-4
DATA BACKUPS	12-5
Introduction	12-5
When To Do A Backup	12-5
Using Tapes	12-5
MTOPS DATA ENTRY - MAIN MENU WINDOW	12-5
File Menu	12-6
Options Menu	12-6
Help Menu	12-7
Buttons on the Main Window	12-7
Select Production/Test	12-7
Double Data Entry	12-8
Toggle for Trial Data / Pilot Data	12-8
MTOPS DATA ENTRY - CASE REPORT FORMS ENTRY SOFTWARE	12-8
Browse Table	12-8
Data Entry Screen	12-8
File Menu	12-9
Mode Menu	12-10
Data Entry Hints	12-10
Saving Entered Case Report Forms	12-11
Deleting a Case Report Form	12-11
Exiting a Case Report Form	12-11
Updating Values in the Different Types of Fields	12-11
Error Box	12-11
Error Handling	12-11
Guidelines for Choosing an Error Code	12-13
Special Instructions for Error Handling	12-13

Mock Randomization	12-14
Randomization Procedure	12-14
PROBLEM/REQUEST LOG	12-14
FOLLOW-UP PSA AND AUA REPORTS	12-15
REPORTS FOR THE MTOPS SYSTEM	12-16
How to Select Reports	12-16
Reports With No Data	12-16
Description of Each Report	12-16
THEME AUDITS	12-21
STATUS DATABASE	12-22
CLINIC STAFF DATABASE	12-22
PAC REPORTS	12-24
REFERENCES	12-29
APPENDIX	12-31

CHAPTER 1: OBJECTIVES AND STUDY DESIGN

INTRODUCTION

This manual of operations describes procedures to be implemented in the study of medical therapy of prostatic symptoms.

PRIMARY RESEARCH QUESTION

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

- I. Clinical progression of BPH, as defined by one of the following:
 1. Acute urinary retention: the inability to urinate requiring catheterization. If the patient has an obvious cause of acute retention other than BPH (e.g., alpha sympathomimetic medications, anesthesia) he should have a trial of catheter removal. If he is still unable to void, he meets the definition of retention. If he can void, it should be recorded as an adverse event, but not counted as an endpoint.
 2. Renal insufficiency due to BPH: a 50% increase from baseline in serum creatinine to a minimum of 1.5 mg/dL.
 3. Recurrent urinary tract infections / urosepsis: two urinary tract infections documented by positive culture, separated by curative antibiotic therapy, within one year or a single episode of urosepsis due to bladder outlet obstruction documented by a positive culture. An interim culture must be performed between the two positive cultures to determine if the first infection was cured, allowing sufficient time after discontinuation of antibiotic therapy.
 4. Incontinence: involuntary loss of urine that is socially or hygienically unacceptable.
 5. Increase in AUA symptom score index: a 4 or more points increase from baseline.
- 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. Patients classified into category I because of an increase in the AUA symptoms 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.

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
3. Medical Outcomes Study (MOS) 36-Item Short Form Health Survey scores
4. Maximal uroflow

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
2. MOS-36 Health Survey scores
3. Maximal uroflow
4. Residual urine
5. Prostate Volume

A major difference 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 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, TRUS and biopsy should not be presented as "optional tests".

STUDY DESIGN

MTOPS is a multi-center randomized, placebo-controlled, double-masked clinical trial in which eligible patients with BPH will be randomly assigned to either of three drug treatment arms or a placebo control. Patients 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.

TREATMENT GROUPS

Patients will be randomized 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

CHAPTER 2: STUDY ORGANIZATION

ORGANIZATIONAL STRUCTURE

MTOPS is conducted by a cooperative effort among the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK), seventeen clinical centers, a diagnostic center (DC), and a biostatistical coordinating center (BCC). The mechanism of funding is a cooperative agreement from the NIDDK.

PARTICIPATING CENTERS

Clinical Centers

There are seventeen clinical centers participating in the cooperative agreement. Each is responsible for the recruitment of patients, managing the patients according to study protocol, implementing all study procedures, and entering all study data.

The seventeen clinical centers are listed in the MTOPS Directory of Participants.

Diagnostic Center

The Diagnostic Center will serve as the central laboratory for MTOPS, and will be responsible for the collection and analyses of serum prostate-specific antigen and hormones and biopsy specimens. It will also serve as the monitor of quality control to assure uniform performance of all invasive procedures among the clinical centers. The Diagnostic Center is:

University of Colorado Health Sciences Center

Biostatistical Coordinating Center

The BCC is responsible for all aspects of biostatistical design, analysis, and data management for the study. The BCC is responsible, in collaboration with the Steering Committee, for development of case report forms, the protocol, and manual of operations. The BCC conducts the interim and final statistical analysis and collaborates with Steering Committee members in the preparation of publications based on the study results. The BCC for this study is:

George Washington University Biostatistics Center

COMMITTEES

Executive Committee

The Executive Committee is responsible for the day-to-day functioning of MTOPS. The Executive Committee is comprised of the Chairperson of the Steering Committee, representatives from NIDDK, and the Principal Investigator of the BCC.

The Executive Committee is listed in the MTOPS Directory of Participants.

Steering Committee

The Steering Committee is comprised of a Principal Investigator from each of the clinical centers (voting members), and the Principal Investigators of the BCC and Diagnostic Center (voting members), the clinic

coordinators, and ad hoc members. A chairperson is named in a non-voting capacity who is not participating in patient care aspects of the trial. Each of the Steering Committee voting 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).

Members of the Steering Committee are listed in the MTOPS Directory of Participants.

Clinical Review Committee

A Clinical Review Committee (CRC) will review the records of patients who reach a primary endpoint, crossover to invasive therapy, crossover to open-label medication, or become inactive to assure adherence to the study protocol. The committee will also provide the final classification of every clinical event that will be used in the statistical analysis. The BCC staff will provide the CRC with appropriately masked patient history summaries. The Co-Chairmen of the CRC will be on call to handle any queries regarding declaring specific endpoint events.

The current members of the CRC are listed in the MTOPS Directory of Participants.

Medication Adherence Committee

Some patients in the study will permanently discontinue the drug treatment regimen prior to administrative censoring. A Medication Adherence Committee (MAC) will review the records of patients who have discontinued one or both coded medications for reasons other than protocol-defined events to assure adherence to the study protocol. The committee will also provide the final classification of every clinical event that will be used in the statistical analysis. The committee will meet periodically to ensure a timely response to clinic staff. The BCC staff will provide the MAC with appropriately masked patient history summaries. Liaisons appointed to the committee will facilitate communication between the committee and clinics.

The current members and liaisons of the MAC are listed in the MTOPS Directory of Participants.

Protocol Adherence Committee

The Protocol Adherence Committee (PAC) will evaluate and provide suggestions for improvement in several protocol issues. More specifically, inactive patients, patients not seen in >150 days, adherence to visit windows, missed biopsies, AUA symptom score rises, and other protocol issues. Liaisons appointed to the committee will facilitate communication between the committee and clinics.

The current members and liaisons of the PAC are listed in the MTOPS Directory of Participants.

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. This committee is charged with reviewing the protocol with respect to ethical and safety standards. The BCC staff will provide the External Advisory Board with analyses. It will report to the NIDDK and make recommendations as necessary. This committee will also be privy to statistical data and case reports which it may require for its deliberations.

The External Advisory Board is listed in the MTOPS Directory of Participants.

SUBCOMMITTEES

Publications Subcommittee

The Publications Subcommittee will review all requests and proposals for scientific presentations,

publications related to MTOPS and make their recommendations to the Steering Committee.

Members of the Publications Subcommittee are listed in the MTOPS Directory of Participants.

CHAPTER 3: PRE-RANDOMIZATION ACTIVITIES

RECRUITMENT STRATEGIES

Coordinators involved in clinical research have the often difficult task of recruiting potential study candidates for clinical trials. Below is a list of patient recruitment strategies that may be helpful.

1. **News release via the public relations office**

This is usually free of charge. This is helpful when recruiting for a study with little or no advertising budget. However, a news release may or may not be picked up by the press, so there is no guarantee of when or where it will be published. The National Institutes of Health will be sending out a national press release to both print and broadcast media. This information will also be sent to each clinic's public relations office.

2. **Paid advertisement in local newspapers or on radio stations**

Responses to paid advertising is usually overwhelming. The cost of advertising in the Sunday edition is usually greater than advertising in the Saturday edition. Saturday advertising yields sufficient patient response, and is more cost effective. Advertising is particularly effective in the sports section of local newspapers as well as minority and community newspapers.

3. **Urology clinics**

Since this clinical trial involves men with benign prostatic hyperplasia, one should target the urology clinic for the bulk of patients. One procedure is to generate a list of patients scheduled for clinic each week. The day before clinic, a brief chart review in medical records of all patient can be done. This is a gross review, highlighting those patients who are coming in for symptoms of BPH. The coordinators should leave notes on their charts to remind the physician that this may be a study candidate. During clinic, the coordinators should ask the staff at clinic check-in to tell the patient not to leave before the clinic coordinator speaks with them and ask the clinic check-out people to make sure that patients identified as potential study candidates have spoken to the coordinator before check-out is completed. If a patient is identified, the coordinator should briefly explain the study and see him for a study visit either at that time or at a scheduled study initiation visit. Before an initial study visit, a complete chart review for eligibility should be done.

4. **Primary care and geriatric physicians**

Active clinical trials can be presented to primary care and geriatric physicians at their weekly meeting. Flyers can be placed in all clinic rooms and in mail boxes of primary care and geriatric physicians.

5. **Emergency room staff**

Emergency room staff should be informed of all clinical trials, by posting flyers and by visiting on a regular basis.

6. **"Hard cards"**

The coordinator can distribute cards that can be carried in the pocket of a lab coat. The cards can include the description and eligibility criteria for a specific clinical trial to all faculty and resident physicians.

7. **Bathroom advertising**

Flyers can be hung above the men's room urinals with tabs that rip off with the name and telephone number of a contact.

8. **Pamphlets**

Pamphlets may be distributed to all prospective patients as well as to physicians.

9. Posters

Posters can have an attached questionnaire asking prospective patients about demographics, prior treatment, the AUA symptom score, etc. They can also have a telephone number contact on strips of paper, which can be torn off.

10. Visibility

Very importantly, referrals can be obtained by maintaining a high visibility within your hospital system. Inform other study nurses about the study.

11. Payroll inserts

Large employers in your area may allow inserts in their payroll or other mailings. A good source may be a health maintenance organization (HMO).

12. Social groups

Some groups (i.e. AARP, churches, etc) may allow inserts in mailings, release of their membership list or presentations made at meetings.

13. Mailing lists

Database sources (e.g. medical administration departments of hospitals and VA centers, university alumni lists, large corporate employee lists) can be searched for male patients 50 years of age or older who live in the area. A listing of names and addresses can then be generated for mass mailings.

14. Health fairs

Representatives from the clinic attending local health fairs can provide information about the study via posters and handouts, as well as screen potential participants by administering the AUA symptoms score questionnaire and asking about prior BPH intervention.

15. Web site advertising

Information about the study can be placed on the clinic or university homepage. Advertisements for the study can also be sent out via the Internet to bulletin boards of interested organizations such as AARP.

The NIDDK has trained specialists to deal with publicity regarding patient recruitment. The publicist is listed in the MTOPS Directory of Participants. NIDDK will be distributing a press release for the full-scale trial.

ELIGIBILITY CRITERIA

For specifics about any of these eligibility criteria, see Inclusion Criteria in Chapter 11, page 3. Patients meeting the following criteria will be eligible for randomization:

1. The patient is a male at least 50 years of age.
2. The patient's 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. The AUA symptom severity score is at least 8, but not greater than 30.
4. The patient has voluntarily signed the informed consent agreement prior to the performance of any study procedures.

EXCLUSION CRITERIA

For specifics about any of these eligibility criteria, see Exclusion Criteria in Chapter 11, page 4. Patients with any of the following will not be considered for the screening evaluation:

1. The patient has had any prior intervention for BPH (either medical or surgical).
2. The patient has received any prior experimental intervention for prostate disease (either medical or surgical) or is presently enrolled in any other study protocol.
3. The patient has had a previous hypersensitivity, idiosyncrasy, or clinically suspected drug reaction to alpha-blockers, quinazoline compounds, or finasteride.
4. The patient has taken an alpha-1 blocker within a year of randomization.
5. The patient has taken phenylephrine, pseudoephedrine, imipramine, an anticholinergic or cholinergic medication within 4 weeks of the 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. The patient has 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. The patient has an inability to urinate.
8. The patient has a supine blood pressure of less than 90/70 mmHg.
9. The patient has 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. The patient has a serum prostate specific antigen level greater than 10 ng/ml.
11. The patient requires the daily use of a pad or device for incontinence.
12. The patient has had an episode of unstable angina pectoris, a myocardial infarction, transient ischemic attack, or a cerebrovascular accident within the past six months.
13. The patient has 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. The patient has a history or current evidence of prostate cancer, bladder cancer, pelvic radiation, urethral stricture, prostate surgery or surgery for bladder neck obstruction.
15. The patient has an 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. The patient has known primary neurologic conditions such as multiple sclerosis or Parkinson's disease or other neurological diseases known to affect bladder function.
17. The patient has had documented bacterial prostatitis within the past year.
18. The patient has had two documented urinary tract infections of any type in the past year.
19. The patient has a severe bleeding disorder which makes a biopsy impossible.
20. The patient has had cancer which is not considered cured (except basal cell or squamous cell carcinoma of the skin). A patient 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. The patient has a diagnosis of a thought disorder (i.e., schizophrenia, bipolar disorder).
22. The patient has a history of alcoholism or any other substance abuse which, in the opinion of the investigator, would affect compliance with the protocol.
23. The patient has any serious medical condition likely to impede successful completion of the long-term study.

CONSENT

If a patient is identified as a good potential candidate, a first screening visit will be scheduled. At that visit, the trial and procedures will be thoroughly explained and the patient will be asked to sign an informed consent form. The informed consent form developed by the Steering Committee will be used as a model. A prototype can be found in Appendix A of the study protocol. Each center will develop its own modifications based on the requirements of its own institutional review board. Whenever a change is made to the protocol, an amendment must be submitted to the IRB for approval.

SCREENING PERIOD

Each coordinator should keep a diary of all pre-screening contacts (SV0) made for the study.

At the first screening visit, the patient will be assigned a screening number. The screening number always begins with a "S" and the clinic's coordinator assigns the numerical portion, preferably in sequence. After the patient has signed the informed consent, the patient will undergo the following procedures to determine eligibility:

1. The AUA symptom score, impact index, and quality of life (QOL) questionnaires
2. A sexual function questionnaire
3. Vital signs
4. Urinary flow rates

5. Serum samples will be drawn (prior to the digital rectal exam).

Samples will be forwarded to the Diagnostic Center for analysis of prostate-specific antigen (PSA) and hormones (in patients receiving biopsies), and for the serum bank. Samples will be kept by the clinical center for a complete hematology and serum chemistry analysis.

6. Urinalysis
7. Physical exam (including digital rectal exam)
8. Medical history

If the patient satisfies the inclusion/exclusion criteria based on the measurements taken in the first visit, he will be scheduled for a second visit. At the second visit, the following procedures will be performed:

1. Vital signs
2. AUA symptom score
3. Health Survey Questionnaire
4. Prostatitis Questionnaire
5. Urinary flow rates
6. Transrectal ultrasound (TRUS).
7. Needle biopsy in patients participating in the biopsy substudy. (Tissue samples will be forwarded immediately to the Diagnostic Center for analysis.)

See Chapter 7 for detailed instructions regarding these screening procedures.

RESCREENING

In the event that a patient is found to be ineligible during screening, the study coordinator has the option to re-screen a patient. Some points to keep in mind when rescreening a patient:

1. Always use the same screening number. Never assign more than one screening number to a patient.
2. All screening procedures must be repeated during the re-screening process. This includes TRUS and blood draws.
3. For patients participating in the biopsy sub-study, the original biopsy is valid after one month and up until three months from the date of the original biopsy. If TRUS/Biopsy is repeated, hormones must be redrawn.
4. Even if the re-screen does not result in a randomization, a re-screen B01, B02 and T02 must be completed and entered into the microcomputer along with any additional forms completed.

MEDICATION RUN-IN PERIOD

After the screening procedures have been completed, and if the patient is still eligible, he will then be put on a doxazosin placebo and a finasteride placebo for two weeks (until the randomization visit). The patient should be instructed to take the placebo as he would the study medication (i.e. take one tablet of each medication each night at bedtime, see *Dispensing* Section in Chapter 5, page 3). **THE PATIENT SHOULD NOT BE INFORMED THAT HE IS TAKING A PLACEBO DURING THIS PERIOD.** Medication run-in should be approximately 14 days and must be at least 7 days (on medication). Compliance will be assessed for this period. If in the opinion of the coordinator the patient successfully completes the run-in period, he may be randomized.

RANDOMIZATION

If the patient is still eligible after Screening Visits 1 and 2 and all baseline procedures, he should return for a randomization visit (with at least 7 days on medication run-in).

Important Note: The screening period (from Screening Visit 1 to randomization) should not exceed 6 weeks (42 days), including the two-week placebo run-in period. **If a patient is not randomized within 6 weeks after Screening Visit 1, the patient must re-enter the screening period in order to be considered eligible for randomization.** (Note: The same screening number must be used when re-screening a patient.)

If the patient is still eligible after the randomization procedures are completed, he will be randomly assigned to a treatment which will be performed using the microcomputer-based randomization component of the remote data management system (see Chapter 9, page 1). The patient is officially randomized when the system discloses the patient's five-digit randomization number. **Coded medications cannot be dispensed until the randomization number is given by the microcomputer.**

SUMMARY OF PRE-RANDOMIZATION CASE REPORT FORMS

Eligibility and Exclusion Inventory (Form B01)

This form is to be completed during the baseline period (i.e. the patient must attend at least the first screening visit).

Screening Visit 1 Inventory (Form B02)

This form is to be completed during Screening Visit 1.

Screening Visit 2 Inventory (Form B03)

This form is to be completed at Screening Visit 2.

Randomization Information (Form B04)

This form is to be completed after the Eligibility and Exclusion Inventory (Form B01) and Screening Visits 1 and 2 (Forms B02 and B03) are completed and the patient is ready to be randomized.

Medication Run-In Information (Form B05)

This form is to be started at Screening Visit 2 and completed approximately 2 weeks later at the Randomization Visit.

Patient Tracking Information (Form T01)

This form is to be completed during the baseline period. It will NEVER be entered into the remote data management system, nor will it be sent to the Biostatistical Coordinating Center. It is confidential and only for the coordinator's

use in tracking randomized patients. This form should be filed with the source documents as it includes confidential patient information.

Recruitment Source Tracking Information (Form T02)

This form is to be completed at Screening Visit 1.

PRE-RANDOMIZATION VISIT SCHEDULE AND PROCEDURES

Screening Visit 0

Each coordinator should keep a diary of all pre-screening contacts (SV0) made for the study.

Screening Visit 1

This is the first pre-randomization visit for MTOPS. The following forms are to be completed:

- B01 - Eligibility and Exclusion Inventory (started, but not completed)
- B02 - Screening Visit 1 Inventory
- Q01 - AUA Symptom Questionnaire
- Q02 - Sexual Function Questionnaire
- T01 - Patient Tracking Information
- T02 - Recruitment Source Tracking Information

The following procedures are to be performed:

- Informed Consent
- Medical History
- Assessment of Adverse Events
- Vital Signs
- Physical Exam
- Flow Rate/PVR
- PSA
- Hematology/Chemistry
- Urinalysis
- AUA Symptom Score Questionnaire
- Sexual Function Questionnaire

For those in Biopsy substudy:

- Hormones (may be drawn at Screening Visit 2)

Screening Visit 2

If the patient is still eligible, this is the second pre-randomization visit. The following forms are to be completed:

- B01 - Eligibility and Exclusion Inventory (additional information completed)
- B03 - Screening Visit 2 Inventory
- B05 - Medication Run-in Information (started)
- P01 - TRUS and Biopsy Information (TRUS only for patients **not** participating in the biopsy substudy)
- Q01 - AUA Symptom Questionnaire
- Q03 - Health Survey Questionnaire
- Q04 - Prostatitis Questionnaire
- R03 - Dispense Label Report (if run-in medication dispensed)

The following procedures are to be performed:

- Vital Signs
- Flow Rate/PVR
- Assessment of Adverse Events
- AUA Symptom Score Questionnaire
- Health Survey Questionnaire
- Prostatitis Questionnaire
- TRUS

For those in the Biopsy substudy:

- Biopsy (Results must be received from the local laboratory prior to randomization)

Note: All of Screening Visit 1 and all of Screening Visit 2 must be completed before the TRUS with or without biopsy is performed.

Randomization Visit

Provided that the patient is eligible at this point, the patient should return for a randomization visit within 6 weeks of Screening Visit 1. The following forms are to be completed:

- B01 - Eligibility and Exclusion Inventory (any missing information completed)
- B04 - Randomization Visit Inventory
- B05 - Medication Run-in Information (completed)
- R03 - Dispense Label Report (if randomized)

The following procedures will be performed:

- Vital Signs
- Assessment of Adverse Events
- Randomization

PROCEDURE FOR REQUESTING RANDOMIZATION EXCEPTIONS

Requests for exceptions should be very rare given the time and thought that went into the development of the MTOPS protocol and its inclusion and exclusion criteria.

To avoid last minute requests for exceptions, the clinic staff should implement several safeguards. The randomization criteria should be checked before the patient leaves from each screening visit. A mock randomization should be performed before the patient is seen for the randomization visit (See Chapter 12, page 14). If a problem is found at the time the data is obtained and before the randomization visit, it will save time for the clinic staff, the patient and the BCC.

The procedure established for requesting an exception to randomization is as follows:

1. **The coordinator calls the BCC to request a Request for Randomization Exception (Form R05).**

It is important that the coordinator call the BCC before requesting an exception from the Clinical Review Committee (CRC). This allows the BCC staff to be aware that an exception has been requested and the BCC can verify that the request is reasonable.

2. **Provided the request is reasonable, the BCC will fax a Request for Randomization Exception (Form R05) to**

the clinic.

3. **The coordinator will complete the form and fax it to one of the Co-Chairmen of the Clinical Review Committee.**

The telephone and fax numbers of the Co-Chairmen are listed in the Directory of Participants.

4. **The CRC Co-Chairman will review the request and fax the response back to the clinic and to the BCC.**

The clinic does not need to fax a copy to the BCC.

If the coordinator would like to check on the status of the request, the coordinator should contact the CRC Co-Chairman directly.

5. **After the coordinator receives the response from the CRC Co-Chairman, if the request is approved, the coordinator will notify the BCC of the scheduled date and time of randomization.**

This call must be made at least 48 hours prior to the randomization of the patient to allow time for the BCC staff to set up the clinic computer for the exception. Therefore, it is not possible to perform an exception on the same day as the BCC is initially called to request the Form R05.

6. **Once the BCC has been informed when the patient attends the randomization visit, all case report forms should be completed and entered in the clinic microcomputer.**

In completing the case report forms, some criteria will be answered in such a way that reflects that the patient is ineligible. Please remember that a granted exception does not mean that the exclusion criteria is ignored, it simply means that even though a criterion is answered such that the patient appears ineligible, the patient still may be randomized.

7. **The clinic coordinators should contact the BCC for instructions on how to perform the randomization.**

Since the BCC staff was contacted 48 hours prior to the randomization, they will be available when the randomization is being performed.

CHECKLIST FOR PREPARING FOR RANDOMIZATION

1. The following forms should be **entered in the microcomputer:**
 - B01** - Eligibility and Exclusion Inventory
 - B02** - Screening Visit 1 Inventory
 - B03** - Screening Visit 2 Inventory
 - B05** - Medication Run-in Information
 - P01** - TRUS and Biopsy Information
 - Q01** - AUA Symptom Questionnaire from Screening Visits 1 **and** 2
 - Q03** - Health Survey Questionnaire
2. For the following criterion, the computer should be checked to verify the values. It is not sufficient to simply have the correct values recorded on the form. There may be keying errors that cause randomization problems.

- a. Form **B01** must be completed, entered and the following information must fit the randomization criteria:
- Section E indicates that the patient will be randomized: questions **E.1**, **E.2** and **E.3** are answered **YES**
- b. Form **B02** must be completed, entered and the following information must fit the randomization criteria:
- Age: Date of visit (question **B.1**) - Date of birth (question **A.4**) \geq **50 years**.
 - Supine blood pressures (question **F.1.a**): systolic \geq 90 mmHg **and** diastolic \geq 70 mmHg
 - No orthostatic hypotension:
 - systolic (question **F.1.a**) - systolic (question **F.2.a**) \leq 20 mm Hg
 - AND**
 - systolic (question **F.1.a**) - systolic (question **F.2.c**) \leq 20 mm Hg
 - AND**
 - diastolic (question **F.1.a**) - diastolic (question **F.2.a**) \leq 10 mm Hg
 - AND**
 - diastolic (question **F.1.a**) - diastolic (question **F.2.c**) \leq 10 mm Hg
 - AND**
 - question **G.1** is answered **NO**.
 - Uroflow: Maximum flow rate, question **I.4** \geq 4.0 **and** \leq 15.0 ml/sec.
 Voided volume, question **I.6** \geq 125 ml.
 - PSA specimen sent: question **K.1** is answered **YES** and question **K.1.a** date recorded.
 - Creatinine: question **M.7** \leq 2.0 (not blank).
 - ALT(SGPT): question **M.11** \leq 1.5 times the upper limit of normal (not blank).
- c. Form **B03** must be completed, entered and the following information must fit the randomization criteria:
- Date: Visit falls between Screening Visit 1 (B02) and Randomization (B04)
 - Supine blood pressures (question **C.1.a**): systolic \geq 90 mmHg **and** diastolic \geq 70 mmHg
 - No orthostatic hypotension:
 - systolic (question **C.1.a**) - systolic (question **C.2.a**) \leq 20 mm Hg
 - AND**
 - systolic (question **C.1.a**) - systolic (question **C.2.c**) \leq 20 mm Hg
 - AND**
 - diastolic (question **C.1.a**) - diastolic (question **C.2.a**) \leq 10 mm Hg
 - AND**

diastolic (question **C.1.a**) - diastolic (question **C.2.c**) \leq 10 mm Hg
AND
question **D.1** is answered **NO**.

- Uroflow: Maximum flow rate, question **E.4** \geq 4.0 **and** \leq 15.0 ml/sec.
Voided volume, question **E.6** \geq 125 ml.

- d. Form **B05** must be completed, entered, and the **date** falls between Screening Visit 1 (B02) and Randomization (B04).
 - e. Form **P01** must be completed and entered into the computer.
 - f. Both Forms **Q01** must be completed, entered, and the AUA symptom scores must be \geq 8 and \leq 30 (page 2).
 - g. Form **Q03** must be completed and entered into the computer.
3. After the previous points have been checked, Form **B04** (Randomization Information) can be entered into the PC. The following criterion must be verified before randomizing:
- Question **B.1** - **B.2** \leq 42 days.
 - Question **B.2** = Form B01, question B.1 = Form B02, question B.1
 - The following questions are answered **YES**: **C.1, C.2, C.3.a-c, C.4, C.5, D.1**
 - PSA, question **D.1.a** \leq 10.0
 - Supine blood pressures (question **E.1.a**): systolic \geq 90 mmHg **and** diastolic \geq 70 mmHg
 - No orthostatic hypotension:
 - systolic (question **E.1.a**) - systolic (question **E.2.a**) \leq 20 mm Hg
 - AND**
 - systolic (question **E.1.a**) - systolic (question **E.2.c**) \leq 20 mm Hg
 - AND**
 - diastolic (question **E.1.a**) - diastolic (question **E.2.a**) \leq 10 mm Hg
 - AND**
 - diastolic (question **E.1.a**) - diastolic (question **E.2.c**) \leq 10 mm Hg
 - AND**
 - question **F.1** is answered **NO**.

CHAPTER 4: FOLLOW-UP AND END-OF-STUDY PROTOCOL

SUMMARY OF FOLLOW-UP CASE REPORT FORMS

Standard Follow-up Visit Inventory (Form F01)

This form is to be completed at all quarterly standard follow-up visits (Months 3, 6, 9, 12, etc.).

Major Follow-up Visit Inventory (Form F02)

This form is to be completed at annual visits and End of Study Visit.

Interim Visit Checklist (Form F03)

This form is to be completed at any visits that are not scheduled follow-up visits.

Missed Follow-up Visit Report (Form F04)

This form is to be completed anytime a patient misses a follow-up visit.

Titration Visit Inventory (Form F06)

This form is to be completed at end-week 3 and end-week 4 titration visits and at any emergency titration visits.

AUA Symptom Questionnaire (Form Q01)

This form is to be completed at every visit, except randomization and titration visits. The patient should complete pages 2 through 3. This form is also available in a Spanish version or it may be given as an interview.

Sexual Function Questionnaire (Form Q02)

This form is to be completed at Screening Visit 1, Major Follow-up Visits and End of Study Visit. The patient should complete pages 2 through 4. This form is also available in a Spanish version or it may be given as an interview.

Health Survey Questionnaire (Form Q03)

This form is to be completed at Screening Visit 2, Major Follow-up Visits, and End of Study Visit. The patient should complete pages 2 through 6. This form is also available in Spanish and interview versions.

Prostatitis Questionnaire (Form Q04)

This form is to be completed at Screening Visit 2, Major Follow-up Visits, and End of Study Visit. The patient should complete page 2.

TRUS and Biopsy Information (Form P01)

This form is to be completed at Screening Visit 2 for all patients. For patients participating in the biopsy substudy, it is also completed at the 12-month Follow-up Visit and the End of Study Visit.

Non-scheduled Biopsy Information (Form P04)

This form should be completed any time after randomization that a biopsy is performed for a patient who is not participating in the biopsy substudy OR for a patient who is participating in the biopsy substudy, but the biopsy was performed outside of the study (i.e. tissue was not processed by the Diagnostic Center). This form should also be completed for invasive therapy procedures that entail pathology reports for prostate tissue taken.

AUA Symptom Score Event Report (Form E01)

This form is to be completed if the patient experiences a 4 point rise in the AUA Symptom Score.

Creatinine Rise Event Report (Form E02)

This form is to be completed if the patient experiences a rise in creatinine of 1.5 times the baseline value to a level of 1.5 mg/dL or more.

Urinary Event Report (Form E03)

This form is to be completed if the patient experiences acute urinary retention, recurrent urinary tract infections or incontinence as defined in the protocol.

Adverse Event Report (Form E04)

This form is to be completed if the patient has had any adverse experiences, drug reactions, side effects, abnormal laboratory values, hospitalizations, other complications or pre-existing conditions that worsened. This form is to be completed for all events reported before March 3, 1997.

Adverse Event Report (Form E05)

This form is to be completed if the patient has had any adverse experiences, drug reactions, side effects, abnormal laboratory values, hospitalizations, medication discontinuation, other complications or pre-existing conditions that worsened. This form is to be completed for all events reported on or after March 3, 1997.

Serious Adverse Event Report (Form E06)

This form is to be completed for any event listed on the Adverse Event Report (Form E05) that is recorded as serious. This form is to be completed for all events reported on or after March 3, 1997.

Normal Range Report (Form R01)

This form is to be completed at the beginning of the trial and any time the clinic laboratory normal ranges change.

Clinical Review Committee Report (Form R02)

This form is to be completed by the Clinical Review Committee (CRC) any time the committee reviews a patient.

Dispense Label Report (Form R03)

All coded medication dispensing labels must be affixed to the appropriate page and section of this form. All forms with alcohol-swab labels will be sent to the BCC after a photocopy has been made and retained on file in the patient's binder.

Missed Biopsy Report (Form R06)

This form should be completed for a patient in the biopsy substudy on active follow-up, any time after randomization that a biopsy should be performed but is not performed. Follow-up biopsies are to be performed at end-year 1 visit, primary endpoint declaration and end-of-study visit. Biopsies need not be performed at the aforementioned visit if the patient has been diagnosed with prostate cancer, has crossed over to known invasive therapy or has had a biopsy within 3 months prior to the visit.

PSA Collection Report (Form R07)

This form should be completed any time after randomization that a serum specimen is collected for Diagnostic Center determination of PSA.

Prostate Cancer Registry Report (Form R08)

This form should be completed for any randomized patient diagnosed with prostate cancer. A copy of the completed form (including attachments) should be sent to the BCC. Any personal identification information should be blacked out on the copy of the attachments sent to the BCC.

Prior Use of Viagra Report (Form R09)

This form should be completed one time for each randomized patient at the first follow-up visit after January 1, 2000 to document the usage of viagra in the past.

Patient Relocation Tracking Information (Form T03)

This form is to be completed any time a patient relocates and will be followed at another clinic. This form should be completed by the clinic from which the patient is moving.

FOLLOW-UP VISIT SCHEDULE AND PROCEDURES

If the patient is randomized, the following follow-up schedule will be adhered to.

Weeks 3 and 4

The following forms will be completed:

- F06 - Titration Visit Inventory
- E05 - Adverse Event Report (if necessary)
- E06 - Serious Adverse Event Report (if necessary)
- R03 - Dispense Label Report (if medication dispensed)

The following procedures will be performed:

- Vital Signs
- Counting returned coded medications
- Dispensing coded medications (increasing doxazosin dose)
- Assessment of Adverse Events

Quarterly Visits

The following forms will be completed:

- F01 - Standard Follow-up Visit Inventory
- Q01 - AUA Symptom Questionnaire
- E05 - Adverse Event Report (if necessary)
- E06 - Serious Adverse Event Report (if necessary)
- R03 - Dispense Label Report (if medication dispensed)

The following procedures will be performed:

- Vital Signs
- Counting returned coded medications
- Dispensing coded medications
- Assessment of Adverse Events
- Flow Rate/PVR
- AUA Symptom Score Questionnaire

Annual Visits (Major Follow-up Visits)

The following forms will be completed:

- F01 - Standard Follow-up Visit Inventory
- F02 - Major Follow-up Visit Inventory
- Q01 - AUA Symptom Questionnaire
- Q02 - Sexual Function Questionnaire
- Q03 - Health Survey Questionnaire

- Q04 - Prostatitis Questionnaire
- E05 - Adverse Event Report (if necessary)
- E06 - Serious Adverse Event Report (if necessary)
- R03 - Dispense Label Report (if medication dispensed)
- R07 - PSA Collection Report

For those in the biopsy substudy at Month 12 Only:

- P01 - TRUS and Biopsy Information

The following procedures will be performed:

- Vital Signs
- Counting returned coded medications
- Dispensing coded medications
- Assessment of Adverse Events
- Flow rate/PVR
- Physical Exam
- PSA
- Hematology/Chemistry
- Urinalysis
- AUA Symptom Score Questionnaire
- Sexual Function Questionnaire
- Health Survey Questionnaire
- Prostatitis Questionnaire

For those in the Biopsy substudy at Month 12 Only:

- TRUS and Biopsy
- Hormones

Additional Forms

- F03 - Interim Visit Checklist (if patient attends a visit other than the scheduled follow-up visits listed above).
- F04 - Missed Follow-up Visit Report (if the patient misses a follow-up visit, i.e., it is not completed within the 3 week visit window).
- E01 - AUA Symptom Score Event Report (if a patient experiences a 4 point rise in AUA Symptom score).
- E02 - Creatinine Rise Event Report (if a patient experiences a rise in creatinine that is 1.5 times their baseline creatinine).
- E03 - Urinary Event Report (if a patient experiences any of the following events: Acute Urinary Retention, Recurrent Urinary Tract Infection or Incontinence).
- E05 - Adverse Event Report (if the patient has had any adverse experiences, drug reactions, side effects, abnormal laboratory values, hospitalizations, other complications or pre-existing conditions that worsened).
- E06 - Serious Adverse Event Report (if the patient has had any adverse experiences recorded on Form E05 that are serious)
- P04 - Non-scheduled Biopsy Information
- R01 - Normal Range Report
- R02 - Clinical Review Committee Report
- R03 - Dispense Label Report
- R06 - Missed Biopsy Report
- R08 - Prostate Cancer Registry Report
- R09 - Prior Use of Viagra Report

T03 - Patient Relocation Tracking Information

Notes on Follow-up Case Report Form Completion

Blood pressure and medication dispensing/compliance information data is collected whenever the patient is seen (titration visits, standard follow-up visits, interim visits). It is important to not duplicate this information by completing more than one of these visit case report forms whenever a patient is seen for more than one "type" of visit. The study coordinator should determine which type of visit is more significant and capture that information on the appropriate visit form. For example, if a patient has been re-challenged, and a titration visit falls within the window of a standard follow-up visit, then the Standard Follow-up Visit Inventory (Form F01) should be completed instead of the Titration Visit Inventory (Form F06).

Note: Generally, an Interim Visit Checklist (Form F03) is only completed if the patient is being seen and it does not fall within the window of the other types of visits (e.g., titration, standard, major).

SUMMARY OF END-OF-STUDY CASE REPORT FORMS

Post End-of-Study Visit Inventory (Form F07)

This form should be completed at any visit that takes place after the end-of-study visit. Separation visits will be scheduled for all patients who attend an end-of-study visit whether or not they are continuing on coded medications.

Final Status Report for Inactive Patients (Form R10)

This form is completed for all patients who are inactive prior to death or the administrative censoring date of November 30, 2001. The purpose of this form is to document the final status of the aforementioned patients as of November 30, 2001.

END-OF-STUDY VISIT SCHEDULE AND PROCEDURES

End of Study Visit

Whenever a patient reaches the end of the study whether it be for an event, or simply completion of the study, the following forms should be completed:

- F01 - Standard Follow-up Visit Inventory
- Q01 - AUA Symptom Questionnaire
- E05 - Adverse Event Report (if necessary)
- E06 - Serious Adverse Event Report (if necessary)

If the patient did not have a major visit within the window June 1, 2001 through August 31, 2001, the following forms will also be completed:

- F02 - Major Follow-up Visit Inventory
- Q02 - Sexual Function Questionnaire
- Q03 - Health Survey Questionnaire
- Q04 - Prostatitis Questionnaire
- R07 - PSA Collection Report

The following procedure will be performed:

- Vital Signs
- Counting returned coded medications

Dispensing coded medications
Assessment of Adverse Events
Flow rate/PVR

If the patient did not have a major visit within the window June 1, 2001 through August 31, 2001, the following forms will also be completed:

Physical Exam
PSA
Hematology/Chemistry
Urinalysis
AUA Symptom Score Questionnaire
Sexual Function
Health Survey Questionnaire
Prostatitis Questionnaire

End-of-Study TRUS and Biopsy:

TRUS with or without Biopsy (TRUS only for patients **not** participating in the biopsy substudy) will be performed either at the 5-year follow-up visit or at the last follow-up visit, whichever occurs first.

The following form will be completed:
P01 - TRUS and Biopsy Information

The following procedure will be performed:
TRUS

For those in the Biopsy substudy an additional:
Biopsy
Hormones

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.

Post End-of-Study Visits and the Separation Visit

Participants who elect to receive coded medications at the last follow-up visit will be assessed for adverse events every 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.

The following forms will be completed:
F07 - Post End-of-Study Visit Inventory
E05 - Adverse Event Report (if necessary)
E06 - Serious Adverse Event Report (if necessary)

The following procedure will be performed:

Vital signs (if not Separation Visit)
Counting returned coded medications
Dispensing coded medications
Assessment of Adverse Events

CHAPTER 5: MEDICAL THERAPY PROTOCOL

ORDERING

McKessonHBOC Clinical and Biological Services (MC&BS) (formerly Ogden BioServices Corporation's Pharmaceutical Repository), hours are Monday through Friday, 8:00 AM to 5:00 PM EST. A pharmacist can be reached at the MC&BS during normal business hours (See Directory of Participants).

McKessonHBOC will be monitoring new as well as continuing patients and will attempt to ship coded medication to the clinic before they are needed. If it is necessary to order medications, the guidelines are as follows. To order drugs, please complete an Agent Request Form and FAX or send it via express mail.

Instructions: Type or clearly print all information except signature. Complete all sections except for box labeled **McKesson Use**. Sign the form in the space provided. All orders received by 2:00 PM EST weekdays will be shipped to arrive 2nd business day, by 4:30 PM. If drug is needed overnight, check "**Yes**" in the Overnight field. If an overnight shipment is needed for Saturday and clinic personnel will be available to receive it, check "**Yes**" in the Saturday field.

Instructions for completing the Agent Request Form appear below. A master copy of the Agent Request Form is located in the Appendix. This standard form should be photocopied and used for ordering agents from the McKesson BioServices (MBS) Pharmaceutical Repository.

Instructions for Completing an Agent Request Form

1. When completing an Agent Request Form, please type or clearly print **ALL** requested information. Data which remains the same from order to order, such as the clinical investigator's name, phone number (top middle of form) and shipping address (lower left of form), should be typed on the original form prior to photocopying.
2. Enter the clinic number, clinical investigator's name, and other required information in the top, middle section of the Agent Request Form.
3. Each line of the order should contain only one item. Complete each line as follows:
 - a. IND number (pre-printed 43,564)
 - b. Patient # (range). Either one patient number or a range of patient numbers can be recorded.
 - c. Agent name, strength, and dosage form (pre-printed)
 - d. Quantity (pre-printed for Titration and Treatment Kits). If requesting Run-In Kits, please record the number of kits needed.

Note: The study medications are supplied as follows:

- 1) Run-in Phase Kits
- 2) Titration Phase Kits
- 3) Treatment Phase Kits

- 4) Retitration Kits (automatically resupplied)
4. ***ONLY*** individuals authorized by the clinical investigator may sign and date the order form.
5. The shipping address must be typewritten. Please avoid using a rubber stamp, since this usually does not yield a sharp image and does not photocopy or transmit well by FAX. To avoid errors in the address, it is better to add the address to the original you will keep for photocopying.
6. The completed Agent Request Form may be FAXed or sent via express courier to the MBS Pharmaceutical Repository address at the top left corner of the form. Please retain a copy of the order; when study supplies arrive, you may want to verify what was received against what was ordered.

TYPES OF KITS

1. **Run-in Phase Kits**

Run-in phase kits consist of one bottle of Doxazosin/Placebo (20 tablets/bottle, red label) and one bottle of Finasteride/Placebo (20 tablets/bottle, blue label) packaged in a box. The kit box is labeled with a kit number.

2. **Initial Titration Phase Kits**

Titration phase medication kits for any patient consists of 5 bottles of Doxazosin/Placebo: one bottle each of Dose A, Dose B, Dose D, and 2 bottles of Dose C (10 tablets/bottle, red label) packaged in a corrugated kit box. The kit box is labeled with the Patient Identification Number.

3. **Treatment Phase Kits**

Treatment phase kits for each patient consist of two bottles of Doxazosin/Placebo: one bottle each of Dose C and Dose D (120 tablets/bottle with a red label) and one bottle of Finasteride/Placebo (120 tablets/bottle with a blue label) packaged in a corrugated kit box. The kit box is labeled with the Patient Identification Number.

After the third budget year, the Treatment Phase kits will contain only 2 bottles (doxazosin/placebo bottle Dose C or D and a finasteride/placebo bottle).

4. **Retitration kits**

Retitration phase medication kits are packaged in the same manner as the initial titration kits and consist of 5 bottles of Doxazosin/Placebo: one bottle each of Dose A, Dose B, Dose D, and 2 bottles of Dose C (10 tablets/bottle, red label) packaged in a corrugated kit box. Please note that the number on the retitration kits does not correspond to any patient numbers. The Retitration kit supply will be automatically replenished when necessary by MBS.

Contact MBS-PSD to determine which kit should be used to retitrate a patient. See the Directory of Participants for the telephone number.

RECEIPT AND STORAGE

When a drug order is received from the MBS Pharmaceutical Repository, it is important that it be inspected as soon as possible. Carefully check items against the packing slip, noting container sizes, quantities, and lot numbers. **The MBS Pharmaceutical Repository should be notified immediately if there are any discrepancies.**

Please place study drugs in an appropriate storage area. This area must be kept separate from routine stock. This storage area should have limited double-locked access.

ACCOUNTABILITY

In order to comply with FDA regulations regarding investigational drugs, each site is required to keep a record of receipts and dispositions of all study drugs received from the MBS Pharmaceutical Repository. This can be accomplished by using the Investigational Drug Accountability Record or an equivalent computerized record. A copy of the Investigational Drug Accountability Record is included in the Appendix. Please retain this form as an original and photocopy for future use.

This form is designed to be used for maintaining perpetual inventories. Each time a drug is dispensed to a patient, or received and/or returned to the MBS Pharmaceutical Repository, an appropriate entry should be made on the Investigational Drug Accountability Record for that drug and protocol. The inventory balance documented on this form should match the actual drug inventory on-hand at all times. It is suggested that a regular schedule be established for a physical inventory, the results of which should be noted on the Investigational Drug Accountability Record. When the recorded balance and the actual inventory are not equal, ascertain the reason and notify the MBS Pharmaceutical Repository pharmacist via memo by FAX or mail. Attach a copy of the memo to the back of the Investigational Drug Accountability Record and retain.

FDA regulations require that drug accountability records must be retained for two years following the date that a New Drug Application (NDA) is approved or, if an NDA is not approved, until two years after the Investigational New Drug (IND) application or study is closed. These records shall be made available, upon request, for inspection and copying by a properly authorized employee, representative, or monitor of the FDA. The Investigational Drug Accountability Record will be kept in the Documents binder provided by the BCC.

DISPENSING

Guidelines

The following guidelines are to be followed when dispensing investigational study drugs.

1. Establish and maintain a mechanism to ensure that study drugs are dispensed in a manner appropriate for the institution.
2. Establish a method to verify that a valid, signed consent form has been received from the patient ***BEFORE*** dispensing the initial study supply.
3. Prepare and dispense the investigational drug in accordance with the IRB-approved protocol.
4. If a patient has study supply remaining from the previous treatment period and the same drug will be used during the next treatment period, that quantity may, at the clinical investigator's discretion,

be included as a part of the next treatment period. Patients should be instructed to bring their prescription bottles with them at the next clinic visit.

If a patient returns drug at a clinic visit, but it will not be used in the next treatment period, the amount of drug should be recorded and then be segregated from the rest of the supply for return to the MBS Pharmaceutical Repository.

5. Instruct the patient and/or appropriate nursing personnel on the correct use of the investigational drug.
6. Document all disposition of the investigational drugs on the Investigational Drug Accountability Record or a computerized equivalent form that is drug and protocol specific.
7. If, for any reason, an investigational drug is mailed to a patient, package and label it properly. Send the package by certified mail with a return receipt or by an express courier with an equivalent method of documenting the receipt of the drug by the patient. (**Note:** It is acceptable to dispense coded medications in advance or mail coded medications for one missed follow-up visit. It is unacceptable to do so for two or more consecutive missed visits).
8. In the event a patient is to receive the investigational drug at another institution, make the appropriate arrangements for redistribution of the drug. For instructions for such redistribution, please contact the pharmacist at the MBS Pharmaceutical Repository for instructions regarding this matter.

Special Notes on Dispensing Doxazosin

Doxazosin must be titrated at the beginning of the study and any time a patient discontinues coded doxazosin for more than 3 days. The titration period is 4 weeks, 1 week on each dose (1mg, 2mg, 4mg and 8mg). These doses will be designated for this study as A, B, C and D, respectively.

If the patient experiences an intolerable side-effect, the dose may be lowered by going back down the alphabet. The patient's final tolerated dose will be administered at the end of titration. Only patients tolerating a 4 or 8 mg dose (dose C or D) will continue to take coded doxazosin for the study. Those unable to tolerate 4 or 8mg, will remain on the study, taking only coded finasteride. Participants who decrease their dosage of doxazosin from 8mg to 4mg may be rechallenged with the 8mg dose at the discretion of the principal investigator. **The patient must be maintained for at least 7 days on the final tolerated dose before the maintenance phase medication is dispensed.**

Special Notes on Dispensing Finasteride

Finasteride does not need to be titrated, therefore the same 5 mg dose will be dispensed for titration and maintenance phases. **In keeping with the known potential risks of contact with crushed tablets of finasteride by pregnant women and women of child-bearing potential, the following precautions should be observed by these women to minimize their direct contact with the study drug:**

1. View contents of the bottle prior to counting to determine if any of the tablets have been crushed.
2. If there are **no crushed tablets**, count the tablets using a pill count tray and a spatula. Gloves may be used if a tray is not available.
3. If there are **crushed tablets**, the use of gloves or tray and mask is strongly recommended.

UNDER NO CIRCUMSTANCES SHOULD THE STUDY DRUG TABLETS BE COUNTED BY A PREGNANT WOMAN.

Dispensing Run-In Medication

For medication run-in dispensing, 1 bottle of 20 tablets of each coded doxazosin and coded finasteride will be dispensed. The patient should be instructed to take 1 tablet of each medication every night at bedtime with water.

Please note that Run-In Medication is numbered with a sequence number. This number does not correspond to any patient number. It is merely used to document which medication was dispensed and returned. All other medication will be identified by patient study number.

Please note that Run-In Medication is not considered coded medication.

Dispensing Titration Medication

For dispensing titration medication, 30 tablets of doxazosin will be dispensed at the randomization visit (initial titration). These tablets are packaged as 3 bottles of 10 tablets (doses A, B and C). The patient should be instructed to take the A dose for the first week, the B dose for the second week and the C dose for the third week. At the End-Week 3 visit, if the patient tolerated dose C, dose D should be dispensed. At the End-Week 3 visit, if the patient did not tolerate dose C, the patient will not be maintained on coded doxazosin, but will be maintained only on coded finasteride.

At the End-Week 4 visit, if the patient tolerated dose D, dose D maintenance phase medication can be dispensed (see *Dispensing Maintenance Phase Medication* section that follows). At the End-Week 4 visit, if the patient cannot tolerate dose D, a second dose C should be dispensed and the patient scheduled for an interim visit in approximately one week. At the interim visit, if the patient tolerated dose C again, then dose C maintenance phase medication should be dispensed. If the patient did not tolerate dose C, the patient will not be maintained on coded doxazosin, but will be maintained only on coded finasteride.

Finasteride will be dispensed as 1 bottle of 120 tablets at the randomization visit. For the subsequent visits during doxazosin titration (weeks 3 and 4) the finasteride should be counted and re-dispensed. For emergency titrations, finasteride should be dispensed as it normally would be according to the *Dispensing Maintenance Phase Medication* instructions that follow.

For both medications at all titration visits, the patient should be instructed to take 1 tablet of each medication every night at bedtime with water.

Dispensing Maintenance Phase Medication

For dispensing at any visits other than run-in and titration, 120 tablets will be dispensed of each coded doxazosin and coded finasteride (1 bottle of each). The patient should be instructed to take 1 tablet of each medication every night at bedtime with water. Patients can be maintained on coded doxazosin at the 4 or 8mg dose (dose C or D).

RETURNS

Study drugs, both used and unused, will be returned to the MBS Pharmaceutical Repository for the following reasons:

- ! The study is completed or terminated

- ! The drug was dispensed to the patient and has been returned to the study site
- ! The drug has expired
- ! The drug has been stored improperly or was received damaged
- ! The drug's return has been requested by the MBS Pharmaceutical Repository pharmacist.

A copy of the Agent Return Form appears in the Appendix. This is a standard form that should be photocopied and used to return all study supplies.

Instructions for Returning Study Supplies to the MBS Pharmaceutical Repository

1. Use a separate Agent Return Form for each site.
2. Complete all sections of the form, ***EXCEPT*** the right-hand section with the heading "FOR McKesson BIOSERVICES USE ONLY" (shaded area).
3. Print or type site address on the form.
4. Only one Agent (study drug) per line. Record one type of kit per line (Run-In kits, Titration kits, Retitration kits, and Treatment kits). There is no need to list the medication by bottle or drug.
5. Full/Partial: Regardless of the number of bottles or tablets being returned: a kit that is complete as shipped, is full; a kit that is not, is partial.
6. Quantity:

For undispensed drugs, please be specific. Enter the total number of dosage units being returned. For example, if returning an unopened bottle of 120 capsules, document this as 1 x 120. For partial bottles indicate the number of tablets or capsules remaining in the bottle.
7. Patient Number (Range): Record the range of patients for whom medication is being returned. It is not necessary to list each individual patient number or to count tablets. For the placebo Run-In kits, please list the lot numbers found on the kits since there is no patient number.
8. Sign and date the form. Please include the site phone number.
9. Remove or obliterate all patient names or identification on patient returns. This practice ensures confidentiality.
10. Enclose **ONLY** those items that the MBS Pharmaceutical Repository provided.
11. Include the completed Agent Return Form in the package. Make a copy of the completed form for your records.
12. ***PACK THE MATERIALS SO THAT THEY WILL NOT BREAK DURING TRANSIT!*** Ship all

items at room temperature, unless otherwise instructed.

13. The MBS Pharmaceutical Repository address is located in the upper right of the Agent Return Form.
14. Send all the Returned Drugs pertaining to MTOPS by Federal Express (Secondary Service).

Note: FedEx account number can be obtained by calling:
Shipping, Director, MBS Pharmaceutical Repository (See Directory of Participants).

CODED MEDICATION UNMASKING

In case of emergencies, clinical sites or others (emergency rooms, physicians' offices, participants, participants' relatives, etc.) may call the MBS emergency telephone number for unblinding of the treatment code. The telephone number is printed on the medication label and provided in the Directory of Participants.

Upon receiving such a call, the MBS technician shall obtain all of the required information and proceed as follows:

1. The MBS technician will contact the MBS pharmacist on call.
2. The MBS Pharmacist will call back the originator of the request to obtain any further necessary information.
3. If the request is made during business hours, the MBS Staff will contact the BCC, who will in turn contact clinic staff to notify them of the situation.
4. Provided that the request is reasonable, the pharmacist will unblind the patient for a specific treatment (doxazosin, finasteride, or both).
5. The MBS Pharmacist will notify the BCC about the unmasking or attempted unmasking within one business day via fax.

CHAPTER 6: PATIENT MANAGEMENT PROTOCOLS

BLOOD PRESSURE MANAGEMENT PROTOCOL

Office Blood Pressure (BP) Measurement

1. For all BP measurements a standard dial or mercury sphygmomanometer will be used with an appropriately sized cuff. Systolic BP will be recorded at the point when the first tapping sounds occur for two consecutive beats (Phase I), and the diastolic pressure at the point when the Korotkov sounds disappear (Phase V).
2. Cuff size and arm used should be established at the initial visit. Throughout the study, BP measurements should be obtained with the same size cuff, from the same arm, by the same individual, if possible, and at approximately the same time of day.
3. BP determinations will be made at each visit. After the patient has been in the supine position for five minutes, a blood pressure reading should be taken. The patient will stand and immediately after standing, one blood pressure reading should be taken. After a 2 minute interval, another reading should be taken. Pulse rate will be recorded before each blood pressure reading.

Standardization of Technique for Accurate BP Measurement

The Patient

Assess the patient for factors affecting blood pressure and employ methods to alleviate them. The patient should be instructed to avoid cigarettes, caffeine, heavy exercise or exposure to cold for at least 30 minutes prior to BP measurement. A distended bladder may also cause a temporary increase in BP. Circumstances causing acute emotional stress cannot always be avoided but should then be recorded as pertinent data.

The Observer

1. Lighting should be adequate and the noise level of the environment controlled.
2. Observer should be aware of the common biases which affect their observation.
 - a. Anticipating the BP may influence the actual reading. Knowledge of the patient's sex, race, age, weight, and prior readings may unconsciously prejudice the observer (i.e., if a patient is a heavy black, middle aged female, a higher reading may be expected).
 - b. Digit preference. Individuals may have a preference rounding to certain numbers - 0 and 5 being the most common.
 - c. Bias at the level which protocol dictates a change in treatment.

On a regular basis, operator should review blood pressures that they have taken in the past to become aware of their own biases and then concentrate on the actual BP being taken at the moment.

The Equipment:

Standard dial or column mercury sphygmomanometer will be used for office readings.

Technique:

1. Patient should be lying in a quiet room at a comfortable room temperature for 5 minutes.
2. Arm used for measurements should be unconstricted by clothes and comfortably supported at heart level.
3. Determine appropriate cuff size. The width of the bladder within the cuff should be 40% of the limb circumference or 20% wider than the diameter of the arm. The length of the bladder should be at least 80% of the arm circumference.
4. Properly sized cuff should be placed smoothly and snugly with the center of the bladder over the brachial artery of the upper arm, 2-3 cm above the antecubital space. (Fold bladder of cuff in half to identify true center.)
5. Inflate the cuff and note the level at which the pulse disappears. Deflate the cuff quickly and completely. This maneuver gives you an approximation of the systolic pressure and reduces the chance of missing an auscultatory gap.
6. Place stethoscope ear tips so that they are directed forward in the ears to exclude extraneous room noise.
7. Palpate for position of the brachial artery in the antecubital space. Position the diaphragm or bell of the stethoscope so that it is lightly touching the skin over the artery. It should be held securely but with as little pressure as possible. To minimize artifact noise, make certain the stethoscope is not touching the cuff or tubing.
8. Rapidly inflate the cuff to raise the indicator 30 mmHg higher than the palpated systolic pressure.
9. Deflate the cuff at a slow steady rate of 2 mmHg/sec.
10. Systolic pressure is determined at the point of hearing the first two regular consecutive Korotkov sounds. (Phase I).
11. Diastolic pressure is determined at the point of the disappearance of sound (Phase II).
12. Listen until the mercury falls at least 20 mmHg below the diastolic reading and then release the valve to 0.
13. Before any re-measurement is performed, wait at least 30 seconds before re-inflation.

Orthostatic Hypotension

For the purposes of this study, orthostatic hypotension will be defined as a decrease of greater than 20 mmHg in supine to standing systolic blood pressure, a decrease of greater than 10 mmHg in supine to standing diastolic blood pressure or the development of significant postural hypotension.

Any patient exhibiting symptoms of orthostatic hypotension at any of the pre-randomization visits (Screening Visit 1, Screening Visit 2 or Randomization) will be excluded from the study. (See the Exclusion Criteria section in Chapter 3, page 3.)

Any patient exhibiting symptoms of orthostatic hypotension during follow-up should return in two weeks for an interim visit to check blood pressure.

EXCLUSIONARY MEDICATIONS

The following medications are not permitted to be taken while participating in the trial. **This listing is not all inclusive.** The absence of a particular medicine from this listing does not imply that it is not an exclusionary drug. All concomitant medications that a patient is taking should be checked to determine that the medications are not exclusionary. When there is a doubt, please consult the Physician's Desk Reference (PDR), a pharmacist, and as a last resort, a Chairman of the Clinical Review Committee. If the patient elects to take an exclusionary medication, a case history must be sent to the BCC.

Medical intervention for BPH listed as an exclusionary criteria includes alpha-blockers and 5-alpha reductase inhibitors. Examples of these two categories are listed below.

Alpha-blockers:

Some examples of alpha-blocker exclusionary drugs include but are not limited to the following:

Cardura	Minipress
Dibenzyline	Phenoxybenzamine HCL
Doxazosin mesylate	Prazosin HCL
Flomax	Tamsulosin
Hytrin	Terazosin HCL

5-alpha reductase inhibitors:

Some examples of 5-alpha reductase inhibitor exclusionary drugs include but are not limited to the following:

Finasteride
Propecia
Proscar

Alpha-agonists:

Some examples of alpha-agonist exclusionary drugs include but are not limited to the following:

<u>phenylephrine HCL</u>	<u>pseudoephedrine</u>
Neo-Synephrine	Comtrex
Dristan	Claritin-D
Entex	Sudafed
	Any decongestant medications

Substitutions for pseudoephedrine: Allegra, Claritin, Seldane, Hismanal, not including the decongestant versions of the exclusionary medicines

imipramine: Imavate, Tofranil (anti-depressant)

Anti-cholinergics:

Some examples of anticholinergic exclusionary drugs include but are not limited to the following:

<u>Anti-cholinergics</u>	
Atropine	Lomotil
Belladonna	
Donnatal	Urised
<u>Anti-depressant</u>	
Amitriptyline	Norpramin
Aventyl HCL	Nortriptyline hydrochloride
Desipramine HCL	Pamelor
Elavil	Tofranil
Endep	Triavil
<u>Anti-histamines</u>	
Benadryl	Diphenhydramine
Brompheniramine	Phenergan
Chlorpheniramine maleate	Promethazine
Chlortrimeton	Seldane D
Clemastine fumarate	Sinusol-B
Dimetapp	Tavist
<u>Anti-emetics</u>	
Antivert	
Chlorpromazine HCL	
Meclizine HCL	
Thorazine	
<u>Anti-parkinsons</u>	
Akineton	Ethopropazine
Artane	Kemadrin
Benztropine mesylate	Parsidol
Biperiden hydrochloride	Procyclidine HCL
Cogentin	Trihexyphenidyl HCL
<u>Anti-spasmodic</u>	
Antispas	Hyoscyamine
Banthine	Levsin
Belladonna	Librax
Bentyl	Methantheline bromide
Clidinium bromide	Methscopolamine bromide
Cystospaz	Oxybutynin chloride
Dicyclomine hydrochloride	Pamine
Ditropan	Pathilon
Donnatal	Robinul
Flavoxate HCL	Tridihexethyl chloride
Glycopyrrolate	Urispas
<u>Miscellaneous</u>	
Atrovent	Eskalith
Carbamazepine	Haldol

Haloperidol
Homatropine hydrobromide
Ipratropium bromide
Isopto homatropine
Lithium

Regonol
Scopolamine HCL
Tegretol
Transderm

Cholinergics:

Some examples of cholinergic exclusionary drugs include but are not limited to the following:

Myasthenia Gravis

Ambenonium chloride
Mestinon
Mytelase

Pyridostigmine bromide
Regonol

Urinary Retention

Bethanechol chloride
Neostigmine
Prostigmin
Urecholine

Miscellaneous

Antilirium
Isopto eserine
Physostigmine

Estrogen Preparations:

Some examples of estrogen preparation exclusionary drugs include but are not limited to the following:

Chlorotrianisene
DES
Diethylstilbestrol
Estradiol
Estraderm
Tace

Androgens:

Some examples of androgen exclusionary drugs include but are not limited to the following:

Andro 100
Depo-Testosterone
DHEA
Fluoxymesterone
Halotestin

Metandren
Methyltestosterone
Ora-Testryl
Testosterone
Virilon

Anti-Androgens:

Some examples of anti-androgen exclusionary drugs include but are not limited to the following:

Aldactone
Cimetidine
Eulexin
Flutamide
Spironolactone
Tagamet

Substitutions for cimetidine/tagamet:

Ranitidine - Zantac; Famotidine - Pepcid; Omeprazole - Prilosec - Losec

Anabolic Steroids:

Some examples of anabolic steroid exclusionary drugs include but are not limited to the following:

Anadrol-50	Nandrolone
Anavar	Oxandrolone
Android	Oxymetholone
Durabolin	Stanozolol
Ethylestrenol	Winstrol
Maxibolin	

CLINICAL EVENTS PROTOCOL

Background

This section defines in detail the medical management of intercurrent complications which ultimately either return the patient to standard protocol (if the condition improves or resolves) or leads to a predefined stop point (i.e., permanent discontinuation of the coded medication). These stop point protocols define the major outcomes or endpoints which will be used as the basis for the statistical analysis of the study. Any time an event occurs, a case history must be sent to the Clinical Review Committee through the BCC.

The protocol stop point definitions apply to all patients randomized into the study. After a stop point has been reached, there will be no further adherence to the coded medication protocol with the exception of those who reach an AUA 4 point rise event, who will be maintained on coded medication at the discretion of the principal investigator. Clinic staff will remain blinded to the coded medication aspects of the study unless there is a life threatening situation which requires knowledge of which group to which the patient was randomized. For all patients reaching a primary endpoint (i.e. AUA 4 Point Rise Event, Creatinine Rise Event, Acute Urinary Retention Event, Recurrent Urinary Tract Infection Event / Urosepsis, or Incontinence Event), that are participating in the Biopsy Substudy, a biopsy should be performed immediately following declaration of the event unless a biopsy was performed within three months prior to the declaration of the event.

Each patient randomized into the study will be followed until the administrative censoring date or death regardless of whether the patient has reached a stop point or has discontinued the randomized therapy. To do otherwise could considerably bias the character of the study groups. Therefore, it is extremely important to document the clinical progress of each patient until the end of the follow-up period.

Questions regarding the clinical interpretation of these significant clinical events or completing the significant clinical event data forms (Forms E01, E02, E03, E05 and E06) should be referred to the Biostatistical Coordinating Center.

Guidelines For Coded Medication Discontinuation

The adverse events associated with finasteride and doxazosin are well-described and generally non-overlapping. Clinical personnel should determine the severity of the adverse event and discontinue or lower the dose of medication based upon an assessment of severity, duration and impact of the adverse event on quality of life.

Adverse events associated with coded medication and discontinuation guidelines:

Finasteride: impotence, ejaculatory dysfunction, decreased libido and gynecomastia have been associated with finasteride, but not with doxazosin.

! Finasteride should be discontinued if these events are reported and are clinically significant.

Doxazosin: dizziness, asthenia, syncope, orthostatic hypotension and peripheral edema have been associated with doxazosin.

! The incidences of these adverse events appear to be dose dependent.

! The goal is to titrate doxazosin up to 8 mg providing no significant adverse events are reported. If the patient develops dizziness, asthenia, or peripheral edema that is clinically significant for the patient, the dose may be reduced from 8 mg to 4 mg.

! If the adverse event persists and remains problematic despite dose adjustment, doxazosin should be discontinued.

Every effort should be made to discontinue coded medication one at a time. Specifically for adverse events likely to be due to either one of the two study medications, it is recommended to discontinue first that particular medication and not discontinue both coded medications at the same time.

If the non-life-threatening adverse event persists following termination of one coded medication, the opposite coded medication should be discontinued.

Guidelines for Coded Medication Rechallenge

The highest priority is to maintain the patient as an active participant in the MTOPS trial. However, a second and almost equally high priority is to keep the patient on coded medication. If the patients' active participation is at stake, discussion regarding retitration should be postponed until the patients' participation becomes more solidified.

Non-life-threatening adverse events which either resolve or persist are always open for discussion regarding retitration. In general, this should involve a discussion of the severity of the adverse event, the risks and benefits involved with the coded medication versus the progression of the disease, etc.

Rechallenge guidelines for discontinuation of one coded medication for adverse event:

! If the drug related non-life-threatening adverse event resolves following termination of the first coded medication:

! Evaluate the patient's symptom score and flow

! If symptom score and/or flow have worsened, suggest rechallenge and emphasize symptom/flow changes

! If symptom score and/or flow remain unchanged, discuss rechallenge

! Offer treatment if sexual adverse event

! Offer titration to level C only for doxazosin

! Conduct a risk/benefit discussion

If the drug related non-life-threatening does not resolve following termination of the first coded medication:

Strongly suggest rechallenge

! Emphasize the lack of the relationship between the adverse event and the drug

! Offer help to further evaluate the adverse event

! Offer treatment if sexual adverse event

Rechallenge guidelines for discontinuation of both coded medications for adverse event:

If the drug related non-life-threatening adverse event resolves following termination of both coded medications:

! Strongly suggest sequential rechallenge of the medication least likely to be offensive

- ! Offer treatment if sexual adverse event
- ! Offer titration to level C only for doxazosin
- ! If the adverse event does not recur, suggest rechallenge of the second medication. After rechallenge of the second medication, if the adverse event does not recur, continue with both medications. If the adverse event recurs, conduct a risk/benefit discussion and determine if medication should be discontinued permanently.
- ! If the adverse event recurs, discontinue the first medication and rechallenge the second medication

If the drug related non-life-threatening adverse event does not resolve following termination of both coded medications:

- ! Strongly suggest sequential rechallenge
- ! If very symptomatic, start doxazosin first, if large prostate gland, start finasteride first
- ! Emphasize lack of relationship between adverse event and coded medications
- ! Offer help to further evaluate the adverse event (e.g., referrals, tests, medications)

The determination of whether or not to advise a patient to restart coded medication should always be based on the investigator's clinical judgement regarding the severity of the adverse event and its causal relationship to the coded medication.

Coded medication should be discontinued if the adverse event recurs following re-challenge and is clinically significant.

Ultimately, patients must be intimately involved in the decisions related to the adverse events that are qualitative and solely related to quality of life.

Description of Clinical Events

For all of the following events, a case history is sent to the CRC through the BCC and the status database is updated.

Clinical Event: Death

This event should be recorded on the Adverse Event Report (Form E05) and Serious Adverse Event Report (Form E06). If possible, an Autopsy Report and Death Certificate should be obtained.

Clinical Event: AUA 4 Point Rise Event (Form E01)

This event is attained when a patient has an increase of 4 or more points from baseline in his AUA symptom score. By protocol, declaration of the event is subject to a confirming symptom score in 2 to 4 weeks from the initial rise. However, an event can be declared if the confirming visit is performed within the window of the next quarterly visit.

For randomized patients, patient identification labels supplied by the BCC will have the patient's AUA 4 point rise event flag as well as other patient identifying information (study number, patient's initials and date of birth).

Patients that reach an AUA 4 Point Rise Event will discontinue coded medications at the Principal Investigator's discretion and continue the scheduled follow-up visits.

If the patient is in the biopsy substudy, TRUS/ Biopsy and hormones should be performed.

Clinical Event: Creatinine Rise Event (Form E02)

This event is attained when a patient has a 50 percent increase from baseline in serum creatinine to at least 1.5 mg/dL. Declaration of the event is subject to a confirming serum creatinine result within 4 weeks from the initial rise and confirmation by the CRC.

For randomized patients, patient identification labels supplied by the BCC will have the patient's creatinine rise event flag as well as other patient identifying information (study number, patient's initials and date of birth).

All patients that reach a Creatinine Rise Event will discontinue coded medications and continue the scheduled follow-up visits.

If the patient is in the biopsy substudy, TRUS/ Biopsy and hormones should be performed.

Clinical Event: Acute Urinary Retention Event (Form E03)

This event is defined as the inability to urinate requiring catheterization. If the patient has an obvious cause of acute retention other than BPH (e.g., alpha sympathomimetic medications, anesthesia), he should have a trial of catheter removal. If he is still unable to void, he meets the definition of retention. If he can void, it should be recorded as an adverse event, but not counted as an endpoint. Declaration of this event must be confirmed by the CRC.

All patients that reach an Acute Urinary Retention Event will discontinue coded medications and continue the scheduled follow-up visits.

If the patient is in the biopsy substudy, TRUS/ Biopsy and hormones should be performed.

Clinical Event: Recurrent Urinary Tract Infection Event / Urosepsis (Form E03)

This event is defined as two urinary infections documented by positive culture, separated by curative antibiotic therapy, within one year or a single episode of urosepsis due to bladder outlet obstruction documented by a positive culture. An interim culture must be performed between the two positive cultures to determine if the first infection was cured (e.g., a negative result), allowing sufficient time for discontinuation of antibiotic therapy. Declaration of this event must be confirmed by the CRC.

All patients that reach a Recurrent Urinary Tract Infection / Urosepsis Event will discontinue coded medications and continue the scheduled follow-up visits including annual GFRs.

If the patient is in the biopsy substudy, TRUS/ Biopsy and hormones should be performed.

Clinical Event: Incontinence Event (Form E03)

This event is defined as an involuntary loss of urine that is socially or hygienically unacceptable. Declaration of this event must be confirmed by the CRC.

All patients that reach an Incontinence Event will discontinue coded medications and continue the scheduled follow-up visits.

If the patient is in the biopsy substudy, TRUS/ Biopsy and hormones should be performed.

Clinical Event: Intercurrent Illness

An intercurrent illness is any concomitant illness or experience (other than the pre-defined events listed

above), defined as clinical signs, symptoms or abnormal laboratory test results known to be related to underlying disease processes or to therapy other than these being studied in this protocol. Consultation with the Clinical Review Committee is required to declare an intercurrent illness event (i.e., stopping the coded medication).

All patients that reach an Intercurrent Illness Event will discontinue coded medications and continue the scheduled follow-up visits.

Clinical Event: Cross-over to Known Invasive Therapy

All cross-overs to known invasive therapy are to be recorded on the Adverse Event Report (Form E05) and Serious Adverse Event Report (Form E06). Please note that once a patient has crossed-over to known invasive therapy, the status can not be reversed.

All patients will discontinue coded medications and continue the scheduled follow-up visits. Any patient who has a diagnosis of prostate or bladder cancer and a subsequent cross-over to known invasive therapy will follow the appropriate abbreviated protocol (see Abbreviated Follow-up for Prostate and Bladder Cancer in Chapter 6, page 13).

Clinical Event: Cross-over to Open-Label Medication

Any time a patient starts taking a known medical therapy: alpha - 1 blocker and/or 5 - alpha blocker.

If a patient starts taking an open-label medication, the patient must discontinue both coded medications. If the patient has been on open-label for less than three months, the open-label medication may be discontinued and coded medications restarted. All patients will continue the scheduled follow-up visits.

Clinical Event: Prostate / Bladder Cancer

Diagnosis of prostate or bladder cancer should be recorded on the Adverse Event Report (Form E05) and Serious Adverse Event Report (Form E06). Until a patient has crossed-over to known invasive therapy, the patient can continue on coded medication at the Principal Investigator's discretion and continue follow-up visits. If a patient has crossed-over to known invasive therapy, coded medications must be discontinued and follow-up visits are continued on the appropriate abbreviated protocol (see Abbreviated Follow-up for Prostate and Bladder Cancer in Chapter 6, page 13).

Treatment Non-Compliance

Patients or physicians may discontinue the patient's coded medication protocol for reasons other than the pre-defined significant clinical events outlined in this chapter. These patients must be urged to continue with the quarterly scheduled follow-up visits, and will be considered treatment non-compliers if they do so. Treatment non-compliers have the option to rechallenge coded medications unless there is less than 6 months until their End-of-Study visit target date.

All patients that reach that discontinue coded medications due to treatment non-compliance will continue the scheduled follow-up visits.

Inactive Follow-up

Patients may have to discontinue follow-up in the study whenever a patient requests to be dropped, moves out-of-town, etc. These patients will be considered as inactive follow-up.

If possible, an End of Study Visit including all procedures, including the TRUS/ Biopsy and hormones for those patients in the biopsy substudy, should be performed.

Summary of Significant Clinical Event Protocols

In summary, all patients that discontinued coded medications will continue the follow-up visit schedule unless the patient becomes inactive. For each clinical event protocol presented in this chapter, the following table outlines the procedures to be followed including the case report forms to be completed, laboratory tests to be performed and follow-up status of a patient that has permanently discontinued the coded medication.

Outline of Clinical Event Procedures

The following is an outline to use as a guideline for information needed, procedures to perform, and case report forms to complete.

DEATH

- Adverse Event Report (Form E05/E06)
- (if possible, Autopsy Report, Death Certificate)
- Case History for CRC
- Update Status Database

AUA 4 POINT EVENT

- AUA Symptom Score Event Report (Form E01)
- (Multiple Visits)
- Coded Medication may be Discontinued
- Continue Scheduled Follow-Up Visits
- If applicable, Adverse Event Report (Form E05/E06)
- If in the Biopsy substudy, perform TRUS with Biopsy (Form P01)
- Case History for CRC
- Update Status Database

CREATININE RISE EVENT

- Creatinine Rise Event Report (Form E02)
- Discontinue Coded Medication
- Continue Scheduled Follow-Up Visits
- If applicable, Adverse Event Report (Form E05/E06)
- If in the Biopsy substudy, perform TRUS with Biopsy (Form P01)
- Case History for CRC
- Update Status Database

ACUTE URINARY RETENTION EVENT

- Urinary Event Report (Form E03)
- Discontinue Coded Medication
- Continue Scheduled Follow-Up Visits
- Adverse Event Report (Form E05/E06)
- If in the Biopsy substudy, perform TRUS with Biopsy (Form P01)
- Case History for CRC
- Update Status Database

RECURRENT URINARY TRACT INFECTION EVENT / UROSEPSIS

- Urinary Event Report (Form E03)
- Discontinue Coded Medication
- Continue Scheduled Follow-Up Visits
- Adverse Event Report (Form E05/E06)

If in the Biopsy substudy, perform TRUS with Biopsy (Form P01)
Case History for CRC
Update Status Database

INCONTINENCE EVENT

Urinary Event Report (Form E03)
Discontinue Coded Medication
Continue Scheduled Follow-Up Visits
Adverse Event Report (Form E05/E06)
If in the Biopsy substudy, perform TRUS with Biopsy (Form P01)
Case History for CRC
Update Status Database

INTERCURRENT ILLNESS

Interim Visit Checklist (Form F03)
Consult CRC
Discontinue Coded Medication
Continue Scheduled Follow-Up Visits
Adverse Event Report (Form E05/E06)
Case History for CRC
Update Status Database

CROSSOVER TO KNOWN INVASIVE THERAPY

Adverse Event Report (Forms E05/E06)
Coded medications discontinued, if they have not been prior to the event
Case History for CRC
Update Status Database
Continue follow-up visits

CROSSOVER TO OPEN-LABEL MEDICATION

Discontinue Coded Medications
Case History for CRC
Update Status Database
Continue follow-up visits

PROSTATE / BLADDER CANCER

Adverse Event Report (Forms E05/E06)
Continue coded medications at PI's discretion
Case History for CRC
Update Status Database
Continue follow-up visits
If crossover to known invasive therapy:
 Coded medications discontinued
 Prostate cancer: Abbreviated follow-up protocol implemented (Forms Q01 & Q03)
 Bladder cancer: Abbreviated protocol implemented:
 If bladder-sparing therapy performed, Forms Q01 & Q03
 If cystectomy performed, Form Q03 (limited abbreviated protocol)

TREATMENT NONCOMPLIANCE

Standard Follow-up Visit Inventory (Form F01) or Interim Visit Checklist (Form F03)
Discontinue Coded Medication
Continue Scheduled Follow-Up Visits
If an adverse event is reported, Adverse Event Report (Form E05, and E06 if serious)
Case History for MAC
Update Status Database

INACTIVE FOLLOW-UP

Missed Scheduled Follow-up Visit Report (Form F04)
If an adverse event is the cause, Adverse Event Report (Form E05, and E06 if serious)
Case History for CRC
Update Status Database
If possible:
 Perform End-of-Study Visit (Forms F01, F02, Q01, Q02, Q03)
 If in the Biopsy substudy, perform TRUS with Biopsy (Form P01)

Abbreviated Follow-up for Prostate and Bladder Cancer

Randomized patients with a diagnosis of prostate or bladder cancer who elect "watchful waiting" will continue their coded medication and scheduled follow-up visits. For patients receiving a known invasive therapy for their prostate cancer or have any bladder-sparing procedure for their bladder cancer, a simplified follow-up protocol will be initiated. This will be limited to the AUA symptom questionnaire administered quarterly and the MOS-36 Health Survey administered at annual visits. For patients who undergo a cystectomy for their bladder cancer, the abbreviated protocol will be limited to the MOS-36 Health Survey only, administered at annual visits. Patients who enroll in a prostate or bladder cancer study will be handled on a case-by-case basis by the CRC. **Please note:** Abbreviated follow-up MUST BE conducted in person in order to evaluate for adverse events and provide good patient care.

Letters to the Record and Clinical Review Committee (CRC) Reports:

The following list of event's require a case history be sent to the CRC:

- Death
- Primary endpoint (AUA 4 Point Rise, Creatinine Rise, Acute Urinary Retention, Recurrent Urinary Tract Infection / Urosepsis, Incontinence)
- Intercurrent illness
- Treatment non-compliance
- Rechallenge (Note: if a patient is rechallenging doxazosin, the CRC letter should be written after the patient successfully retitrates)
- Inactive follow-up
- Unmasking of coded medications
- Medication dispensing error
- Reactivation
- Crossover to open-label medication
- Crossover to invasive therapy
- Exclusionary medications
- Randomization error

Please note that several events require confirmation with the CRC Chairman. These events include the three urinary endpoints, creatinine endpoint, intercurrent illness stop point, and other miscellaneous events with odd

circumstances. A clarification of the steps to follow is listed below:

1. Notify CRC Chairman in writing.
2. Response is received from the CRC Chairman.
3. Send letter to the Record (through the BCC) noting the event and confirmation status along with attachments of written communication between clinic and CRC Chairman.

It is important to note for documentation purposes that 'date medication discontinued' refers to the day after the patient's last dose was taken. Also medications referenced in a letter should start with coded or open-label to clarify the type of medication the patient is taking. Additionally, a new letter must be written for additional information added to an previous letter (e.g., addendums on old letters is not acceptable).

After a patient is reviewed by the Medication Adherence Committee or the Clinical Review Committee, a CRC Report (Form R02) is completed and sent to the clinic. These reports should be reviewed for accuracy. If additional information is required by the Committee, a letter will be sent to the clinic regarding the information that is needed.

ADVERSE EVENT REPORTING

Guidelines for Coding Adverse Events:

In order to code adverse events, it is important to understand the definition of an adverse event and how the concept of treatment emergent factors into reporting and coding adverse events.

Treatment Emergent Adverse Event Definition:

Adverse Event - Any adverse experiences, drug reactions, side effects, abnormal laboratory values, hospitalizations, other complications or worsening of pre-existing conditions.

Treatment emergent - Any event not present prior to exposure to study medications or any event that has worsened either in frequency or intensity following exposure to study medications.

General Adverse Event Coding Guidelines:

The adverse event report (Form E05) has been designed to report one event or syndrome per line (maximum of 12 events). Each event must be documented on a separate line to insure that information for each event is collected in a way that will facilitate accurate characterization of the event.

Serious Adverse Event Encoding Guidelines:

The serious adverse event report (Form E06) has been designed to report with greater detail any event listed on the corresponding Form E05 that is considered to be serious in nature (e.g., death, hospitalization, permanent or severe disability, congenital abnormality, cancer, life-threatening, due to overdose, or treatment to prevent a serious event).

Coding Diagnoses versus Symptoms:

If a treatment emergent diagnosis, in addition to associated symptoms, is described on single line, the diagnosis should be encoded as the Glossary Term.

If a single line does not identify a diagnosis but rather contains only a symptom, such as nausea, headache, fever, body-aches, code the symptom as reported.

Avoid "over-splitting" events:

When encoding AEs, make sure that related symptoms of a diagnosis are not reported nor encoded on more than one line (i.e., "over-splitting" events). For example, if a patient experienced nasal congestion and sore throat which were

both diagnosed as symptoms of an upper respiratory infection, one (1) line on Form E05 completed documenting the Upper Respiratory Infection as the event and describing the symptoms of nasal congestion and sore throat.

Coding Laboratory Abnormalities:

It is important when encoding AEs which report laboratory abnormalities, to encode the specific lab abnormality whenever possible.

Coding Injuries/Accidents:

All injuries/accidents which occur during MTOPS are considered treatment emergent adverse events and must be reported on an AE form.

Coding Falls:

If patient experiences a fall which is secondary to another medical event, code the medical event which caused or resulted in the fall, but do not code the fall itself as an event. On the other hand, if there is no plausible medical explanation for the fall, then the fall must be coded in addition to any injury received secondary to the fall. The rationale behind coding all falls for which there is no medical explanation provided, is to insure that we can detect a potential syncopal and/or vestibular effect which might be related to a drug.

Coding Events with Procedures/Elective Procedures:

Medical Procedures:

Medical procedures are not considered adverse events. Medical procedures performed as treatment for an adverse event are the action taken to treat the event. If an underlying condition worsens to the point that a medical procedure is required, the worsening of the underlying condition is reported and coded as the event. The procedure is included in the description of the treatment of the event.

Elective procedures undergone for reasons other than worsening of underlying condition are not treatment emergent events and should be documented in source document only but **not** coded as an **AE**. For example, tooth extraction*, mole excisions, bunion surgery, etc., if done as elective procedures and not due to worsening underlying condition, should be documented in the source document but not coded as treatment emergent adverse events.

How to handle reports for which you cannot tell what the adverse event is:

In the unlikely event that you are unable to find an appropriate COSTART term for an adverse event, and encode a classification term that does not appear in the table, a message will appear on the screen and be automatically sent to the printer. This information should be faxed to the BCC.

Reporting Serious Adverse Drug Experiences:

In order to facilitate timely reporting of certain adverse drug experiences to the FDA, an Adverse Event Report (Form E05/E06) should be filled out completely and FAXed IMMEDIATELY to the Biostatistical Coordinating Center for the following events:

Any **SERIOUS** adverse event regardless of cause. **SERIOUS** is defined as:

- A. Fatal or life-threatening
- B. Permanently or severely disabling
- C. Requiring or prolonging inpatient hospitalization
- D. A congenital anomaly or cancer
- E. Due to an overdose
- F. Treatment to prevent a serious event

If the event is **SERIOUS**, whether or not it is listed in the Investigator's Brochure or the U.S. package insert, call the BCC immediately upon completing Forms E05 and E06 to notify them that the forms are coming. Forms E05 and E06 should be submitted even if the event is not considered related to the coded medication. A complete description of the event, including final assessment and diagnosis, should also be included. If an Adverse Event Report is sent completed for an event which led to a discontinuation of medications, then a case history must be written for the Medication Adherence Committee and sent to the BCC. If medications are discontinued without any underlying adverse event, then only a case history must be written for the CRC and sent to the BCC (no Adverse Event Report is required).

When new information is obtained in follow-up to a serious adverse event or worsening of a previously reported serious adverse event, a new Form E05 and a new Form E06 are completed (as a "follow-up" report). Remember if the initial report is serious, then follow-up reports are also serious because additional information is gained concerning the original event.

PATIENT ADHERENCE

Retaining Patients on Clinical Trials

To maintain validity, inactive follow-up must be kept to a minimum. The study coordinator can enhance patient retention by developing a good rapport with each patient and his family. The following are some suggestions for developing rapport:

- ! Keep clinic time to a minimum. Patients should be seen at their scheduled time.
- ! Facilitate contact by providing the patient with a business card or pamphlet with business hours and telephone number.
- ! If necessary, identify another family member to help remind the patient to take the medications and keep clinic appointments.
- ! Write a letter explaining the study and the patient's treatment regimen to the patient's primary care physician in order to ensure cooperation and maintain study compliance and participation.
- ! If possible, contact patients between scheduled visits (i.e. by telephone, letters, or birthday cards).
- ! Use open-ended questions to see how the patient is feeling.
- ! Listen to the patient's concerns and give him ample opportunity to ask questions.
- ! Identify and resolve any problems (e.g. upcoming vacation) that may cause the patient to miss any future visits in order to maintain study involvement.
- ! Write thank-you notes for the patient's efforts and continued commitment to the study, while reiterating the value of his continued participation.

Keep the patient well-informed of what to expect by doing the following:

- ! Explain the patient's role by describing the tests which will be performed at each visit, the need to

fast prior to having blood work, special preparations before a TRUS with or without biopsy, the approximate amount of time each visit will take, where to come for the visit, and the necessity of knowing the names of concomitant medications he has taken.

- ! Discuss with the patient the importance of taking both medications at bedtime, what to do if doses are missed, the need to bring the study medications to each visit, and the importance of not sharing medications with anyone else.
- ! Provide patients with a telephone number which to call if problems arise between visits.
- ! Review the program of follow-up visits with the patient lending some emphasis on the differences between the standard and major visit examinations at the follow-up visits.

Often patients in a clinical trial have many needs. A coordinator should listen to these needs, and refer patients to other clinics when appropriate. Mechanisms for speedy consultation should be arranged for patients who develop serious medical illnesses during the study. Particular effort must be made to ensure that patients feel as involved and cared for as patients receiving other treatment and medical care.

In addition to the suggestions noted above, the Protocol Adherence Committee developed a set of guidelines to retain patients in the study.

Protocol Adherence Guidelines:

A. Proactive Physician Involvement

- ! Annual visit conducted by a study physician
- ! At each visit assess patient health concerns and offer to schedule an appointment with a study physician
- ! Arrange physician contact at current visit or return appointment any time patient shows concerns regarding biopsy, symptoms, or medication side effects

B. Routine Scheduling Strategies

- ! Schedule return appointment at current visit or within 48 hours
- ! Use a calendar or appointment book to monitor and prepare for upcoming visits
- ! Make reminder calls 24 hours before all scheduled appointments
- ! Update patient contact information (Form T01) at each visit
- ! If patient transferred to another clinic, maintain contact until patient attends appointment at that clinic

C. Missed Visit Follow-up

- ! Phone contact on date of missed visit or within 2 working days of missed visit
- ! Mail follow-up letter within 5 working days of missed visit
- ! Follow-up phone contact within 5 working days of letter
- ! Within 10 working days of missed visit, P.I. and S.C. review case and develop a customized plan for ongoing contact

Potential Options:

If no contact:

- attempt to contact family or send registered letter
- plan repeat contact attempt by phone and/or mail within 2 weeks
- record contact due dates in calendar or appointment book

If contact:

- assess barriers such as time, transportation, parking, health

- phone call from P.I.
- “Social” call to cultivate rapport without discussing study requirements
- Birthday and holiday cards
- plan repeat contact by phone and/or mail
- record contact due dates in calendar or appointment book

D. Patients Not Seen in > 150 Days

- ! P.I. and S.C. review new patients on list each week
 - ! Contact new patients on list to assess concerns
 - ! Update plans for customized ongoing patient contact
- Potential Options:
- If no contact:
 - attempt to contact family or send registered letter
 - plan repeat contact attempt by phone and/or mail within 2 weeks
 - record contact due dates in calendar or appointment book
 - If contact:
 - assess barriers such as time, transportation, parking, health
 - phone call from P.I.
 - “Social” call to cultivate rapport without discussing study requirements
 - Birthday and holiday cards
 - plan repeat contact by phone and/or mail
 - record contact due dates in calendar or appointment book
- ! Fax patient report and CRC letter for any new patients to PAC liaison each week
 - ! Phone consultation with PAC liaison for patients selected by liaison or study coordinator

E. Patients Not Seen for Two Consecutive Visits

- ! P.I. and S.C. review new patients on list within one week
 - ! Contact new patients on list within two weeks to assess concerns
 - ! Update plans for customized ongoing patient contact
- Potential Options:
- If patient moves and is not being seen at another clinic:
 - Maintain periodic telephone contact with patient or family
 - Send cards, newsletters, gifts, etc. to new address
 - Attempt to schedule follow-up visit when patient visits family
 - If no contact:
 - attempt to contact family or send registered letter
 - plan repeat contact attempt by phone and/or mail within 2 weeks
 - record contact due dates in calendar or appointment book
 - If contact:
 - assess barriers such as time, transportation, parking, health
 - phone call from P.I.
 - “Social” call to cultivate rapport without discussing study requirements
 - Birthday and holiday cards
 - plan repeat contact by phone and/or mail
- ! Phone consultation with PAC liaison for patients selected by liaison or study coordinator
 - ! Send summary letter to PAC requesting case review before discontinuing efforts to establish or maintain contact with patient.

Patient Relocation Procedures

When a patient informs the coordinator that he will be moving out of town, if the location to which he is relocating is in the vicinity of another MTOPS clinic, the following steps should be followed:

- ! The Coordinator helps to determine if a clinic is located near the patient's new home. This may involve contacting the possible new coordinator.
- ! Once determined that it will be possible to follow the patient at a different clinic, the current coordinator informs the BCC staff.
- ! BCC staff faxes the Patient Relocation Tracking Information (Form T03) to the current coordinator.
- ! Current coordinator completes the Patient Relocation Tracking Information and faxes it back to the BCC. A procedures checklist on the CRF includes making copies of all relevant paperwork and sending it along with any coded medication supply to the coordinator at the new clinic.
- ! When the patient is first seen at the new clinic, the most recent Informed Consent should be signed.
- ! After the patient actually attends a visit at the new clinic, the new coordinator informs the BCC staff of this visit.
- ! The BCC staff will then transfer the data entered to the new clinic microcomputer and set up the data entry software to accept the patient's forms.
- ! BCC staff will inform the new clinic coordinator that data entry should be performed for the relocated patient.

Patients who have relocated will maintain the same randomization number but the screening number will change to help identify the patients that have moved. The screening number for relocated patients will begin with a 9 followed by their current three digit screening number (e.g. S9___).

CHAPTER 7: PROCEDURES PROTOCOLS

UROFLOWMETRY PROCEDURE

All uroflows must have voided volumes of at least 125 ml in order to be valid.

Since all of the clinics will be using Dantec uroflow machines, the following directions are applicable.

1. Calibration should be set to 50 ml/sec. To calibrate the Dantec Urodyn 1000 flowmeter, press MANUAL START/STOP and UROFLOW INTERPRETATION buttons simultaneously for 1 second (gives access to change sensitivities between 25 ml/sec and 50 ml/sec).

At the prompt, pressing UROFLOW INTERPRETATION changes the sensitivity from -25 to 50 ml/sec. SET TO 50 ML/SEC. (**Note:** While the sensitivity function is in effect, the MALE indicator flashes).

2. Calibration is done, once monthly, by pouring 400 ml of water into the uroflow transducer. It should be done within a period of 10-30 seconds to accomplish a relatively even flow. The START/STOP indicator is lit when the flow is detected. The end of flow is automatically detected. (**Note:** while the calibration function is in effect, the FEMALE indicator flashes).

Calibration results in one of three messages:

- a. **Success:** A message confirms the calibration giving a calibration index.
 - b. **Calibrate again:** If the calibration deviates more than 8% from the previous calibration, another calibration is necessary.
 - c. **Not accepted:** If the calibration deviates too much, a warning is printed and then function is ended.
3. Power Up: When the power button is pressed, a self test by the machine is performed. When the power light stops flashing, and becomes constant the machine is ready for use. (**Note:** if error messages do occur, refer to the manual for specific instructions.)
 4. The patient should come for his visit with a full bladder. The patient should be instructed to urinate into the white funnel. The machine will automatically record at the initiation of flow and terminate recording at the end of micturition.

RESIDUAL VOLUME PROCEDURE

There are a number of bladder scan machines which will be utilized in the study. However, the most widely used machines are the BVI 2000 and the BVI 2500. Instructions for both of these machines follow.

Bladderscan BVI 2000 System

1. Turn on the machine.
2. Apply firm pressure on the scanhead so that the rounded surface is in contact with the patient and is covered

with an adequate amount of gel for good conductivity.

3. Measure the longitudinal axis, holding the scanhead straight up and down with the "SCAN/SAVE" button facing the patient's feet.
4. Hold the probe in place without moving except to locate bladder borders. The scanhead should not be lifted. You may have to tilt the scanhead so that it reads under the symphysis pubis. If you need to tilt the scanhead, hold the angle of tilt for the rest of the longitudinal scan.
5. **In small increments**, and **waiting briefly** at each step for the machine to complete its scan and update the image, **move the scanhead slowly** across the patient in a line from 9 o'clock to 3 o'clock, until a point is reached approximately 3 inches to the left or right of the midline. During the scan, note which location gives the largest and best bladder image. Return to that location, and fine tune the scan by reproducing a clear, full, curvilinear image centered on the left side of the screen. Images will not be perfectly ellipsoidal. **Hold the scanhead motionless**, maintaining that image for two consecutive, numerically close readings, then press the "SCAN/SAVE" button on either the front panel or the scanhead until a "beep" tone is heard.

NOTE: Accurate results depend on obtaining two consecutive, largest diameter readings. To do this, it is mandatory that the scanhead be held motionless for two display cycles with numerically close readings, before the "SCAN/SAVE" button is pushed.

Do not lift the scanhead from the patient between the longitudinal and transverse scans. If contact is broken, wipe the gel off the patient and the scanhead, and reapply new gel. This will minimize the chance of producing artifacts in the image.

6. To begin the transverse scan, rotate the scanhead so that the "SCAN/SAVE" button faces the operator (3 or 9 o'clock). Place the scanhead midline and proximal to the symphysis pubis; and again, using firm pressure, move the scanhead **slowly** and **in small increments** along the midline toward the patient's head (12 o'clock). When the largest and best image has been located and fine tuned with the largest diameter reading; **hold the scanhead motionless**, maintaining that image for two consecutive, numerically close readings; then press the "SCAN/SAVE" button until the "beep" tone is heard. The system will then display the calculated volume in cubic centimeters.

NOTE: When the "SCAN/SAVE" button is pressed again, the previous date is erased, and the BladderScan is ready for a new measurement.

Bladderscan BVI 2500 System

1. Within 15 minutes following the uroflowmetric procedure, ask the patient to lay down on an examination table in a supine position.
2. Apply generous amounts of ultrasound contact gel to suprapubic area and also put gel on the scanhead.
3. Turn the Bladderscan on and press "SCAN".
4. Place the scanhead in a 90° angle to the surface of the skin in the suprapubic area. Position the scanhead such that the "B" side points towards the patient's feet, and the "A" side towards the patient's head. Store at least five images of the bladder in the longitudinal axis by simply pressing "SCAN" on the scanhead five different times. All images will be stored in the memory of the instrument. The current image will also be displayed in

the window. Attempt to adjust the aim of the scanhead until the largest possible diameter of the bladder in the longitudinal axis is displayed on the screen. After you have successfully stored five images, press "AXIS COMPLETE".

5. Rotate the scanhead 90° to measure the second diameter. Place the scanhead such that the "B" side points towards the patient's right side and the "A" side towards the patient's left side. Store at least five images by pressing "SCAN" on the scanhead. Adjust the aim of the scanhead until the largest possible diameter is displayed on the screen. After you have successfully stored five images, press "AXIS COMPLETE".
6. After you press "AXIS COMPLETE", the Bladderscan instrument will display the largest stored images in each of the two planes alternating. It will also display the volume calculated from these two largest images. If you are satisfied with these results and there appears to be no artifact (see below), press "PRINT" now to print out the results. Record the volume on the appropriate case report form and keep the printed images in the patient's medical record.
7. If the stored image with the largest diameter has an artifact (usually an unrepeatable large diameter caused by movement of the scanhead during the storage of the image) press "EDIT". Choose which plane has the artifact by pressing "HORIZ", "LONG", or "BOTH". Mark the artifactual image by pressing "ART". The next largest image in that plane will then be shown. Either accept it by pressing "ACCEPT" or mark it as an artifact also. Once you have accepted an image in each plane, the Bladderscan displays the accepted images and a volume corrected after the deletion of artifacts.
8. After you are satisfied with the images displayed for both the horizontal and longitudinal axis, print the results by pressing "PRINT". Record the volume on the appropriate case report form and keep the printed images in the patient's medical record.

SERUM COLLECTION FOR SERUM PSA AND HORMONES

1. **ALWAYS WEAR GLOVES WHEN DEALING WITH BLOOD.**
2. Draw blood from patient into two 10 ml red/gray Serum Separator Tubes (SST) tubes.
3. Allow blood to clot for 30 minutes.
4. Centrifuge for 12 minutes allowing the serum to separate from the clot and a gel barrier to form in the middle. **Note:** Due to variations in centrifuges, it may be necessary to spin the tubes longer or faster to achieve the desired ratio of equal volumes of serum above and clot below the separator gel.
5. Transfer serum into the vials and secure the top on the vials.
6. Dispose of the tube and the clot.
7. **WRITE THE PATIENT'S INITIALS, PATIENT NUMBER AND THE DATE OF COLLECTION ON THE SERUM VIAL.**
8. Prepare the vials for shipping to the Diagnostic Center, according to the instructions in the kits that were sent to you.

9. These specimens must be **FROZEN** immediately or placed on dry ice in preparation for shipment.

FREE PSA TESTING

If the investigator feels the need for a free PSA ratio for patient management after the initial PSA results are received, the test can be performed on study through the Diagnostic Center. Under no conditions should this test (or any other PSA test) be performed by a laboratory other than the Diagnostic Center. To perform a free PSA, the following steps must be completed:

1. The patient will return for a second blood draw (Chapter 7, Page 3) which should be documented in the same manner as an annual PSA draw (Chapter 8, Page 3).
2. The Diagnostic Center will run the tests once each week.
3. The data will be transmitted to the BCC weekly.
4. The BCC will report new total PSA and % free PSA to the clinic.

URINALYSIS PROTOCOL

Equipment:

1. Gloves
2. Receptacle for the urine
3. Chemstrip 9 or 6 (whichever your clinic uses)
4. Watch with second hand

Methodology:

1. Put gloves on.
2. Collect freshly voided specimen into the receptacle.
3. Dip the Chemstrip into the urine. If it is kept too long in urine the substances on the dipsticks may become overly saturated which will result in an inaccurate reading.
4. Wait the appropriate time as stated on the bottle and record the results. Precise timing is essential or the color changes are meaningless. For example, glucose and ketone test areas are so sensitive that over-timing by 1-3 seconds will demonstrate falsely high amounts of the substance.
5. If the dipstick is positive for blood or leukocyte esterase (WBC), then send a specimen for a microscopic urinalysis.

Reminders:

Check the dipstick bottle to make sure the top is securely tightened, if moisture gets to the sticks before it is used, it could give a false-positive reading. Certain drugs give false-positive readings.

SERUM COLLECTION FOR HEMATOLOGY AND CHEMISTRIES

Equipment:

- | | |
|----------------------|--------------------|
| 1. Gloves | 4. Tourniquet |
| 2. Vacutainer | 5. Blood Tubes |
| 3. Vacutainer needle | 6. Alcohol Sponges |

7. Band-Aid

8. Dry 2x2 Sponges

Methodology:

1. Put on gloves.
2. Apply tourniquet to desired arm approximately three inches above the antecubital space.
3. If vein does not become palpable with application of tourniquet, either have patient make a tight fist or lightly tap arm over vein.
4. Remove cap from vacutainer needle and screw needle into vacutainer.
5. Cleanse skin over desired vein with alcohol sponge, then swab with dry 2x2.
6. Insert needle into vein with bevel up.
7. Press collecting tube until stopper has been punctured.
8. Each tube should be completely filled before changing tubes.
9. To change tubes, stabilize vacutainer with one hand and remove filled tube with the other hand. Compress the new tube, being careful not to dislodge needle from vein. Repeat this procedure until tubes are filled.
10. Tubes with anti-coagulants should be gently rotated to mix thoroughly with blood to prevent clotting, immediately after tube is filled and removed from vacutainer.
11. When last tube is filled, release tourniquet, pull tube out of vacutainer, place dry 2x2 sponge over site of needle entry and remove vacutainer and needle.
12. Maintain pressure over site for approximately 1 minute. May also have patient hold arm above heart level with pressure on site to prevent formation of hematoma.
13. Remove gloves.

Hematology Profile

1. Draw blood from patient into one 7 ml lavender tube.
2. Immediately invert the tube 12-15 times.
3. Label the tube according to your local laboratory protocol.
4. Fill out the appropriate requisition for complete blood count, place it in an appropriate bag and take to your laboratory for processing.
5. **REMEMBER THAT YOU NEVER PLACE A CBC IN A CENTRIFUGE.**

Chemistry Profile

1. Draw blood from patient into one 10 ml SST red/gray tube.

2. Allow blood to clot for at least thirty minutes but not longer than one hour.
3. Prepare the tube according to the instructions of the laboratory that will be processing it.
4. Fill out the requisition and take it to the lab. You will have to complete the requisition according to what chemistry test it will take to cover all the tests required in the protocol i.e., Chem 20 or 24.

TRANSRECTAL ULTRASOUND OF THE PROSTATE

Patient Preparation

The patient should be examined in the lateral decubitus position or, as a minimum, the position standardized from procedure to procedure.

Equipment

It is preferable to use the Bruel & Kjaer or Dornier transducer for the study ultrasounds. If a different probe is used in the study, this information will be indicated on the TRUS and Biopsy Information (Form P01).

Procedure

The transrectal probe should be introduced with adequate lubrication. Multiple longitudinal and transverse images of the prostate should be obtained to rule out obvious hypoechoic lesions. Longitudinal and transverse images of the prostate should be captured on hard copy images and kept in the patient's file.

Prostatic Volume Measurements

Multiple images should be obtained to insure that the widest transverse diameter of the gland is in the field of view. This frame should then be frozen and the prostatic width and height obtained, using the cursor for linear measurements (Figure 1A and 1B, see Chapter 7, page 7). The probe should then be switched to the longitudinal position and a midsagittal view of the prostate obtained. The height of the prostate should be measured in its widest anterior/posterior diameter (Figure 1C, see Chapter 7, page 7). The length of the prostate should then be obtained from the bladder neck to the prostatic apex (Figure 1D, see Chapter 7, page 7). In the transverse mode, the ellipsoid volume should be determined using the method built into the machine. Briefly, the widest transverse image of the gland is obtained, the outer perimeter outlined with the cursor and then the width of the prostate measured (Figure 1A, see Chapter 7, page 7).

An identical procedure should be followed for the transition zone volume determinations (Figure 2, see Chapter 7, page 8). All data should be immediately recorded on the case report form. Additional comments on the transition zone, surgical capsule, and peripheral zone should be obtained.

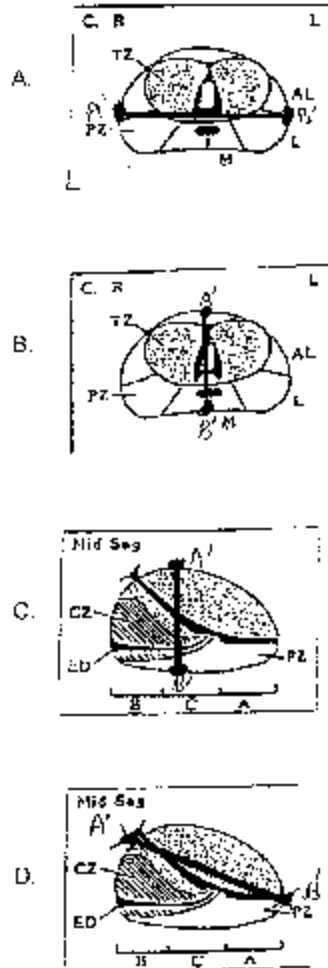


Figure 1: Measurement of total prostatic volume by TRUS.
A. Transverse view - width
B. Transverse view - height
C. Longitudinal (sagittal) view - height
D. Longitudinal (sagittal) view - length

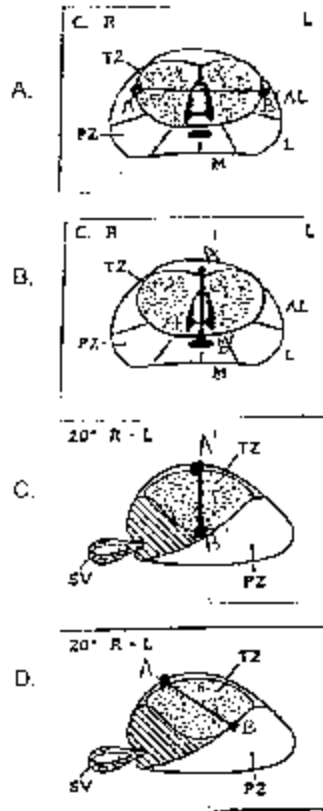


Figure 2: Measurement of prostate transition zone volume by TRUS.
A. Transverse view - width
B. Transverse view - height
C. Longitudinal view - height
D. Longitudinal view - length

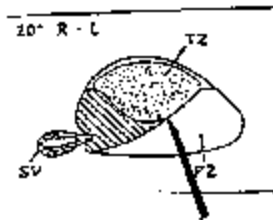


Figure 3: Technique for transition (TZ) biopsy. The biopsy needle should be manually advanced through the peripheral zone (PZ) under ultrasound guidance. The Biopsy gun is then fired to obtain a core of TZ tissue.

BIOPSY

Patient Preparation

The patient should be given a cleansing enema prior to the procedure. Antibiotic coverage should be given if concomitant biopsies are planned. The antibiotic coverage protocol is at the discretion of the investigator, but an oral quinolone before the procedure and several days afterward is recommended.

Equipment

All biopsy cores are obtained by standard spring loaded biopsy device under TRUS guidance. It is strongly recommended that for patients in the biopsy substudy, the same transducer be used for all biopsies for a particular patient.

Biopsy Procedures

Each patient will undergo three biopsy procedures: after Screening Visit 2, at the 12-Month Visit, and either at the 5 year follow-up visit or at the last follow-up visit, whichever occurs first. If a patient reaches a primary endpoint, an additional biopsy will be performed at confirmation of the endpoint. If a patient is due to have a biopsy at any of the aforementioned time points, it need not be repeated if a biopsy was performed within the prior three months. Identification of prostatic regions, i.e., peripheral zone (PZ) or transitional zone (TZ), is performed by TRUS imaging. Biopsy procedures will provide 6 cores of tissue as follows:

- ! 2 core biopsies from the mid peripheral zone (PZ), 1 right and 1 left.

Each tissue core is placed on a non-adhesive surface. The deepest end of each core (the end nearest the needle tip) is marked by green ink (provided). Each core is separately placed in a labeled container filled with 10 percent formalin as described in detail in the Anatomic Pathology section in Chapter 8, page 1.

- ! 2 core biopsies from the transition zone (TZ), 1 right and 1 left.

Each tissue core is placed on a non-adhesive surface. The deepest end of each core (the end nearest the needle tip) is marked by green ink. Each core is then placed in a labeled container filled with 10 percent formalin, as described in the Anatomic Pathology section in Chapter 8, page 1.

- ! 2 additional core biopsies from the transitional zone (TZ), 1 right and 1 left.

The technique for transition zone biopsy necessitates advancement of the biopsy needle through the peripheral zone to the edge of the transition zone prior to firing the Biopsy gun (Figure 3, see Chapter 7, page 8). The deepest end of each core (the end nearest the needle tip) is marked with green ink. Each core is frozen by placing it in a container, covering it with OCT compound and freezing on dry ice as described in detail in the Anatomic Pathology section in Chapter 8, page 1.

Special Procedural Notes

Any hypoechoic lesions identified in the peripheral zone (PZ) should be biopsied and sent to the Diagnostic Center with the standard biopsies. 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.

All the biopsy cores will be submitted to the Diagnostic Center. Following processing by the Diagnostic Center, representative sections of all cores (frozen and formalin fixed) will be shipped back to the clinical center for local

pathology review. Results must be obtained from the local pathologist prior to randomization. A copy of the local pathology report is forwarded to the Diagnostic Center.

For patients in whom a clinical suspicion of prostate carcinoma exists, i.e.; abnormal DRE, TRUS, PSA and/or PSA density, additional biopsies may be obtained at the discretion of the investigator, to supplement the aforementioned biopsy material. All supplemental material will also be submitted to the Diagnostic Center. Representative sections of the supplemental cores will be shipped back to the clinical center for local pathology review.

For all of the aforementioned biopsies, the Diagnostic Center will provide clinical centers with shipping kits which will include containers, fixative and shipping instructions for collected samples. Details regarding shipping instructions are provided in the Anatomic Pathology section in Chapter 8, page 1.

CHAPTER 8: DIAGNOSTIC CENTER

ANATOMIC PATHOLOGY (Tissue Biopsies)

General Considerations

All tissues from this study are to be archived for potential research uses. It is imperative, therefore, that optimal preservation be obtained. To assure that this is the case the following general guidelines should be observed:

1. Do not break needle biopsies into fragments.
2. Do not crush specimens with instruments such as forceps, instead transfer specimens on the end of the wooden applicator stick (provided).
3. Never allow tissue fragments to air dry.

All transfers of tissue into fixative (formalin) or freezing containers should be done as quickly as possible.

TZ and PZ formalin-fixed biopsies

After the biopsy specimen is obtained it should be transferred to the surface of a sterile nonabsorbent paper surface (such as the inside of a surgical glove wrapper or a small piece of Telfa pad). The end of the tissue that was at the tip of the biopsy needle should be marked with a small dab of green ink (provided). Each biopsy (Right PZ, Left PZ, Right TZ, Left TZ) is placed in a separate formalin filled bottle (provided) and labeled with the patient's identification number (if before randomization, record the clinic number and the screening number; if after randomization, record the study number), anatomic site and date. The bottles are then placed into the foam insert within a shipping box (provided) along with a "dri-mop" pad (provided) to absorb any spilled formalin solution. The box is then placed inside a large zip-lock bag (provided) with another "dri-mop" pad and inserted into a clear plastic Federal Express Diagnostic Pack Envelope. Do not use a standard "Courier Pack".

When the attending physician feels it is medically necessary, more than the required four biopsies may be submitted for formalin processing. They should be collected as described above, placing each biopsy into a separate formalin filled container labeled with the standard information (patient identification number, date) and the anatomic location of the biopsy site. Be specific (e.g. "hypoechoic lesion at left apex" or "palpable nodule from right prostatic base"). Any additional biopsies would be placed into the same shipping box and bag with the four required biopsies.

TZ Frozen biopsies

It is very important to carry out this portion of the protocol as quickly as possible to avoid deterioration of the specimen. As soon as the biopsy core to be frozen is obtained it should be transferred to a piece of glossy paper as previously described. The end of the biopsy fragment that was at the tip of the needle should again be marked with green ink. The biopsy should then be carefully laid out onto the inner surface of the transparent plastic specimen boat (supplied) and quickly covered with OCT compound (provided). The boat is then placed directly onto the surface of a block of dry ice and the OCT compound is allowed to freeze until it has become opaque white. The specimen boat is then transferred to a small zip-lock bag which is labeled with the patient's identification number (if before randomization, record the clinic number and the screening number; if after randomization, record the study number), and the anatomic site (i.e. Left TZ or Right TZ). Repeat the process for the frozen biopsy from the other side. When finished, each zip-lock bag should have only one specimen cryobag in it. Do not put anything else inside this bag. Put all the frozen specimens in bags into a larger zip-lock bag. After sealing the outer bag quickly transfer it to a styrofoam shipping box (provided) that has been filled with finely broken-up dry ice. The specimens should never be allowed to thaw after they have been frozen. Refer to the "Frozen Sample Transportation" section of this chapter for shipping details.

Pathology Reports

You will receive back from the Diagnostic Center a set of microscope slides stained with hematoxylin and eosin, accompanied by a preliminary report. These slides must be taken to your Pathology Department for review and final diagnosis. The slides do not need to be returned to the Diagnostic Center. Once your Pathology Department has completed their exam, FAX a copy of the surgical pathology report to the Diagnostic Center.

LABORATORY MEDICINE (Serum Specimens)

The Diagnostic Center will provide the following supplies in a serum collection kit: transfer pipettes, specimen labels, aliquot tubes, cryotubes, and styrofoam mailing containers with boxes.

For routine screening visits and routine annual visits, sera will be collected for PSA measurement and for archival purposes as described below. For screening visits, the results will be faxed to the clinic by the Diagnostic Center. For any follow-up PSA results, the BCC will fax the report to the clinic. For patients taking coded finasteride, this report will include a PSA value that is determined by the masking algorithm described in the protocol. Only the BCC should be contacted to obtain the follow-up PSA results.

1. Collection Information: Collect sample in red top vacutainer tubes (SST is acceptable). At least 3 ml of cell-free serum should be collected.
2. Sample Preparation:
 - a. Allow blood to clot completely.
 - b. Centrifuge 10 minutes at 1400 g (not RPM--see note at end of this chapter) at room temperature.
 - c. Aliquot 1 ml of serum into clear plastic tube provided.
 - d. Aliquot the remainder of the serum in 0.5 ml increments into the short cryotubes provided.
3. Sample Labeling:
 - a. Clearly write the patient identification number (if before randomization, record the clinic number and the screening number; if after randomization, record the study number) and collection date on each label.
 - b. Affix white "Archive" labels to as many small cryotubes as were filled.
 - c. Affix lavender "PSA-Hybritech" label to the clear plastic tube.
4. Sample Stability and Storage:

Freeze all samples as soon as possible. Samples for PSA are stable indefinitely when frozen at -20 or -70 degrees Centigrade. Do not thaw sample and refreeze. Samples are not stable after repeated thawing and refreezing.

For patients who will undergo prostate biopsies, serum will be collected at the time of the biopsy for other hormones in addition to the serum for PSA and Archive. Methods for collecting this sera are described below.

1. Collection Information: Collect sample in red top vacutainer tubes (SST is acceptable). At least 3.5 ml of cell-free serum should be collected.
2. Sample Preparation:
 - a. Allow blood to clot completely.
 - b. Centrifuge 10 minutes at 1400 g (not RPM-- see note at end of this chapter) at room temperature.
 - c. Aliquot 1 ml of serum into one clear plastic tube provided.

- d. Aliquot 2.5 ml of serum into the other clear plastic tube.
3. Sample Labeling:
 - a. Clearly write the patient identification number (if before randomization, record the clinic number and the screening number; if after randomization, record the study number) and collection date on each label.
 - b. Affix blue "Testos & LH" label to the clear tube containing 1 ml serum.
 - c. Affix yellow "BPHDHT" label to the plastic tube containing 2.5 ml serum.
 4. Sample Stability and Storage:

Freeze all samples as soon as possible. Samples are stable for one month when frozen at -20 or -70 degrees Centigrade. Do not thaw sample and refreeze. Samples are not stable after repeated thawing and refreezing.

A Principal Investigator may request a special free and total PSA test. This special test is in addition to the serum for PSA and archive which is collected at an annual visit, and should be collected after results are obtained from the annual visit. Methods for collecting these sera are described below.

1. Collection Information: Collect sample in red top vacutainer tubes (SST is acceptable). At least 1 ml of cell-free serum should be collected.
2. Sample Preparation:
 - a. Allow blood to clot completely.
 - b. Centrifuge 10 minutes at 1400 g (not RPM-see note at end of this chapter) at room temperature.
 - c. Aliquot 1 ml of serum into clear plastic tube provided.
3. Sample Labeling:
 - a. Clearly write the patient identification number (the study number) and collection date on each label.
 - b. Affix green "BPH f/t PSA" label to the clear tube containing the 1 ml serum.
4. Sample Stability and Storage:

Freeze all samples as soon as possible. Samples for PSA are stable for one month when frozen at -20 or -70 degrees Centigrade. Do not thaw sample and refreeze. Samples are not stable after repeated thawing and refreezing.

SHIPPING INSTRUCTIONS

When any specimen is to be shipped, the MTOPS Diagnostic Center Requisition Form (see Appendix) must be filled out completely and FAXED to the Diagnostic Center. All current fax numbers (including back-up numbers) can be found in the Directory of Participants or the Who to Call for What List. It is important that the Requisition Form shows the information from any frozen tissue submission as well as from any fixed tissue submissions, since they each have unique air bill numbers that will be used to track specimens should they not arrive as expected. The Form must be transmitted to the Diagnostic Center by FAX at the time that the specimens are shipped. The requisition form should always reflect the actual date that the specimen was collected. One requisition form should be completed for each collection date. Clinics should always keep a copy of the requisition form as well as FedEx air bills on file.

Send all specimens by Federal Express. The Diagnostic Center provides a FedEx account number for billing purposes. Please call the Diagnostic Center for this information. Clinics should contact their local FedEx office for

shipping labels, shipping bags and dry ice labels.

FORMALIN FIXED TISSUE TRANSPORTATION

Tightly capped formalin vials, placed in the foam support provided inside the sturdy white box may be sealed in a ziplock bag with a single "dry-mop" pad. This can be placed directly into a clear plastic FedEx Diagnostic Pak and sealed. Two to four boxes can fit inside one Diagnostic Pak if needed. The completed FedEx air bill is placed in the plastic airbill pouch and attached to the outside of the Pak.

FROZEN SAMPLE TRANSPORTATION:

The styrofoam shipping containers must be completely filled with dry ice. Dry ice must be broken into quite small pieces so that the frozen specimens will be completely covered even if the package shifts during shipping.

1. Send samples on dry ice with Federal Express according to current IATA regulations. The regulations are described in bold type followed by the steps taken to meet the regulations.
 - a. **The sample must be contained within a watertight primary container.**
In this case, the aliquot tube is a primary container.
 - b. **There must be a watertight secondary container with absorbent and cushioning material around the primary container.**
A plastic bag holding the tube(s) with an absorbent pad and 5 pounds of dry ice, sealed in a styrofoam box with strapping tape, constitutes the secondary container.
 - c. **The secondary container must be placed in a stronger outer package.**
The cardboard shipping box around the styrofoam container, sealed shut with strapping tape, becomes a stronger outer package.
 - d. **Packages must have appropriate warning labels.**
Attach the black and white "dry ice" label (obtained from FedEx) and write the weight of the enclosed dry ice on the label.
2. Specimens should be sent Monday through Thursday unless special arrangements are confirmed by telephone with Diagnostic Center personnel. Please check with the Diagnostic Center for their holiday schedule. Do not select Saturday delivery.
3. The Clinical Laboratory Requisition Form must be FAXED to the Diagnostic Center at the time of shipment. The mailing address is listed in the Directory of Participants.

PLEASE REMEMBER THAT THE ROOM NUMBER MUST BE CLEARLY LEGIBLE to ensure proper delivery.

Centrifugation Note: "g" force is calculated as follows:

$$g = 11.17 (r) [N/1000]^2$$

where r = average radius in cm of the centrifuge head

N = revolutions per minute

CHAPTER 9: BIOSTATISTICAL COORDINATING CENTER

REMOTE DATA MANAGEMENT SYSTEM

Clinical Centers

The remote data management system (DMS) for MTOPS is designed to collect study data, to assist study staff in management of the MTOPS protocol, and to provide rapid data transmission to the BCC. Data are entered into a microcomputer database at each of the seventeen clinics and transmitted weekly to the BCC via micro-to-micro communication using the software package Norton PC Anywhere (Symantec). Each clinic is responsible for maintaining its own database, and for entering corrections to the data.

Study data are written onto standardized case report forms and are subsequently entered into the remote DMS by a clinic data manager using the data entry software provided by the BCC. Extensive data editing is performed to ensure data quality by incorporating edits in the data entry system (e.g., omissions of required fields, invalid ranges of data items, and inconsistencies within that form and between forms). As the data are being entered, if any of these suspected problems are detected, the computer will prompt the data entry person. If the problem was a typographical error, the data entry person may simply correct the error by re-keying that data point. If the data being entered are correct, the person may provide an explanation by using an error code or "comment" flag. These comments are sent along to the BCC with the weekly transmission of data.

All corrections to the entered data, whether generated by the clinic staff or the BCC staff, are made at the clinics. Newly entered or updated data are transmitted to the BCC on a weekly basis. Thus, the data entered at the clinic is always identical to the data at the BCC, except for any data added during the week following the previous transmission. To ensure that the remote DMS performs to specifications within each clinic, the BCC provides the microcomputer hardware and software for use at the clinics, which are dedicated exclusively to the activities of MTOPS. Clinic adherence to this "closed-system policy" should reduce the possibility of computer viruses and other security risks. The BCC has developed the software for this system in-house and will distribute and maintain new releases of the customized software for MTOPS whenever changes are made to the data collection instruments. The remote DMS is "user-friendly", in the sense that the clinic staff is not required to have technical knowledge of microcomputers nor previous experience in the use of data entry software.

Specific Tasks

The tasks listed below are performed through the remote DMS:

1. Data entry and updating will be monitored for quality and accuracy through an editing system comprised of range and missing value checks on individual fields and inter-field consistency verification.
2. Patient randomization by computer.
3. Entry and deletion of test data, for data entry training sessions and PC Certification.
4. Double data entry, which will be used to enter all study data and by the clinical coordinators to monitor the performance of data entry personnel. Reports of key stroke errors or discrepancies during these sessions will also be transmitted to the BCC for monitoring purposes.
5. Standard reports from the database to facilitate data management, or to accommodate reporting requirements of individual clinics.

6. Scheduling of visits will be facilitated by software that will have the capability of indicating future follow-up visits based on an individual patient's randomization date.
7. Data transmission to the BCC on a weekly basis of all newly entered or updated records. Through an automated telecommunications system, data will be retrieved overnight by a dedicated microcomputer at the BCC from the seventeen clinics consecutively. Norton PC Anywhere (to be used for data transmission) has a proprietary, error free compression protocol yielding speed and accuracy, and a routine for re-dialing in cases of non-response or interrupted transmission. Additionally, the customized system at the BCC will check for complete transmission of all files.
8. Utilities which will allow the BCC to monitor data entry sessions at remote sites in order to trouble-shoot software performance.
9. Database back-up to tape or diskette.

System Support

User support of the remote DMS for MTOPS is guaranteed by the BCC. The RDM technical programmers will be available to field calls from the clinics. To assist with problem solving, the BCC also has the ability to dial up a clinic's microcomputer and view files on the system, as well as observe data entry in progress.

Configuration

The basic IBM hardware components of the microcomputer workstation supplied to each of the seventeen clinics participating in MTOPS will be:

- Dell Pentium III
- 550 megahertz with 128 mbram
- Windows 98
- hp Laserjet 1100 xi printer
- internal tape backup
- external 56k modem

The complete system is configured with the necessary RDM software at the BCC, and is completely tested at the BCC, prior to shipment to the seventeen clinics.

Security

Telecommunications access will only be possible after caller identification is established through a valid password. In order to secure the equipment, it is recommended that either locks be put on office doors or that locking devices be used to attach the computer to its table. It is the clinic's responsibility to ensure the security of the equipment.

Diagnostic Center

A microcomputer remote DMS will also be established at the Diagnostic Center. Like the remote DMS for the seventeen clinics, the Diagnostic Center remote DMS is used to report the results of analyses and interpretation to the BCC. The Diagnostic Center remote DMS is supported by the BCC and includes the following features:

1. Data entry of serum and pathological tissue results
2. Interpretation of radiologic studies and results from quality control specimens; updating of entered data

3. Reports listing inventories of specimens
4. Patient-specific hard copy reports of analysis results for distribution back to the clinics
5. Quality control reports for review by the Diagnostic Center staff
6. Data transmission to the BCC on a weekly basis
7. Database back-up to tape

CENTRALIZED DATABASE MANAGEMENT SYSTEM

The BCC has a centralized database management system (DMS) which is set up to edit incoming data and update the study master database. After data are transmitted weekly from MTOPS clinical sites by the dedicated microcomputer at the BCC, they will be uploaded to the Biostatistics Center's IBM 4381 mainframe computer. The incoming data will be edited for errors using programs written in SAS. After editing, the data will reside in SAS data sets (i.e., MTOPS master database) which can be immediately used for statistical analysis. Consequently, there will be minimal delay between receipt of the incoming data and its availability for statistical analysis.

Editing Procedures

Distributed data entry files will be edited centrally after receipt by the BCC. The centralized DMS edits will be printed on a computer generated edit report (one report for each form with any suspect items). The edits detected by the centralized DMS will be compared with the comments (error codes) entered by the data-entry person at the clinic. The remaining edits will be forwarded (mailed or faxed) to the clinic for review by the coordinator. Upon receipt of an edit report (example, see Appendix), the clinic coordinator will respond to each suspect item in the following manner:

1. Review the edit report (see Specific Notes for Completing Edit Reports below), the case report form in question and the patient's chart, if necessary, to identify the problem reported.
2. Make any changes or corrections to the data, by completing the 'Revised Value' line or 'Check if Value OK' space.
3. The clinic coordinator must initial each page of an edit.
4. The corrected edit report is then used to update the information in the microcomputer.
5. Only corrected edit reports with permanently missing or invalid items need to be faxed to the BCC.
6. File the corrected edit report in the patient binder behind the last page of the corresponding Case Report Form.

Specific Notes for Completing Edit Reports

On an edit report, two types of explanations for the edit are given in order to facilitate the resolution of the error, 'Problems' and 'Comments':

Problems

These are categories of errors identified by the master data base editing procedure run at the BCC.

Missing Value

The field was left blank, when a value is required.

Value out of Range

The value falls out of a specified range. These ranges are defined to identify grossly discrepant values. **Note:** these ranges are not normal ranges.

Must be Blank

A value was entered when the field should have been left blank.

Inconsistent with other data on this form

The value is incorrect when taking into consideration other information on the form (i.e., orthostatic hypotension is somewhat dependent on the blood pressure readings).

Summing or calculation error

An error has been made in the calculation of this value.

Discrepancy between error code and edit

An error code was entered in the clinic microcomputer and the edit program at the BCC did not identify an error or did not edit the field (e.g. A laboratory value was temporarily missing, so an 'EC?' was entered into the computer. The BCC editing program does not edit that laboratory value, therefore can find no problems with the data. This would cause a discrepancy: BCC shows no error, clinic shows temporarily missing or invalid.).

Comments

These are error codes entered in the clinic's microcomputer by the person keying the form.

Known temporarily missing or invalid response (Corresponds to Error Code '?')

This comment indicates that a '?' was recorded on the case report form signifying that the data was temporarily missing or invalid and would be completed or corrected in the future.

Known permanently missing or invalid response (Corresponds to Error Code '@')

This comment indicates that an '@' was recorded on the case report form signifying that the data is permanently unavailable or invalid. The edit will be forwarded to the clinic for the coordinator to verify that the information is permanently missing.

Response is missing with no explanation for error (Corresponds to Error Code 1)

This comment indicates that the nurse did not record a value and therefore the person keying the form entered an EC1. The coordinator should provide the appropriate missing value by completing the edit report.

Response keyed as coded, no explanation for error (Corresponds to Error Code 2)

This comment indicates that the keyer entered the data on the case report form and for some reason it is considered invalid by the editing system. After checking the case report forms and the patient's chart, if it is determined that the value is correct, then 'Check if Value OK' space. Otherwise provide the correct value on the edit report.

Response cannot be read, so field is left blank (Corresponds to Error Code 3)

This comment indicates that the keyer could not read the response. Consult the source documentation to decipher the response and complete the missing value on the edit report.

More than one response, so field is left blank (Corresponds to Error Code 4)

This comment indicates that there was more than one response made to a question that requires only one response, therefore the field was left blank. This code should be entered when there is more than one answer indicated but only one answer is allowable.

Verifying a Permanently Missing or Invalid Field

If a field is marked permanently missing or invalid (EC @), an edit report will be sent to the clinic for verification. To verify a permanently missing or invalid field, the clinic staff should check all relevant files. If the data is permanently missing or invalid, the clinic staff should check the 'Check if Value OK' space and mark an '@' on the 'Revised Value' line. This will indicate to the BCC that the permanently missing or invalid field has been verified. A brief description should be included on the edit explaining why the information is permanently missing or invalid. Once the '@' sign has been recorded on the edit, the '@' sign should be entered in the computer immediately. To verify this is completed, the comment line on the edit should read 'known permanently missing or invalid response'. Please note that whenever a value is coded as permanently missing/invalid on an edit and the value is obtained at a later date, the BCC should be notified and the edit returned to the BCC requesting that the '@' sign be removed. An explanation should include why it was coded as permanently missing/invalid and how the data was later obtained.

Responding to a Temporarily Missing or Invalid Field Edit

If a field has been marked temporarily missing (EC?), it is not necessary to respond to the edit until the correct value is obtained (i.e. until the status changes).

Theme Auditing Procedures

Data will be audited centrally at the BCC to detect any discrepancies, missing information, or errors in the data collection. Theme audits will be printed on a computer generated report and sent to the clinic as needed. The theme audits will be forwarded (mailed or faxed) to the clinic for review by the coordinator. Upon receipt of a theme audit report (example, see Appendix), the clinic coordinator will respond to each theme audit in the following manner:

1. Review the theme audit report, all case report forms in question, Diagnostic Center Requisition forms, and the patient's chart, if necessary, to identify the problem reported by the BCC.
2. Make any changes or corrections to the case report forms (see General Instructions for completing case report forms, Chapter 11, page 1) or to the Diagnostic Center Requisition form. If the Diagnostic Center Requisition form is corrected, send the corrected copy to the Diagnostic Center indicating a change has been made.
3. Enter any changes or corrections to the case report forms in the microcomputer.
4. All theme audits must be returned or faxed to the BCC. The coordinator may choose to establish a separate file for all theme audit reports for future reference.
5. If the theme audit appears to be unresolvable, the coordinator will fax the audit report back to the BCC with a note explaining the problems encountered. All theme audit reports faxed to the BCC must be initialed by the coordinator.

PERFORMANCE MONITORING

Training Workshop

The BCC has established procedures to train and certify clinical coordinators in MTOPS data processing procedures. Prior to the initiation of recruitment for the 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. The BCC will maintain close contact with the clinic coordinators and will provide additional training or review as needed.

Appropriate representatives (i.e., coordinators, data-entry staff) will be certified by the technical programmers of the BCC. Staff of the BCC will be available to train new study personnel, if there is a turnover of clinical center staff. Only personnel certified by the BCC will participate in data management at the clinic for the full-scale study.

Clinical Coordinator Certification

Provisional Certification

1. The clinic coordinator must have read the protocol and manual of operations.
2. The clinic coordinator must attend the coordinator's training and both the coordinator and data manager must attend microcomputer training.
3. The clinic coordinator must have successfully completed the protocol/manual quiz as verified by the BCC.
4. The clinic must have developed a recruitment plan including procedures for eligibility screening and submitted them to the BCC.
5. A copy of IRB approval and informed consent (and any amendments or changes) must be sent to the BCC.
6. Normal laboratory ranges must be obtained (Form R01) and submitted to the BCC.

Full Certification

7. A review of the baseline forms will be performed by the BCC staff for the first four randomized participants. All screening period case report forms for the four patients must be copied and mailed to the BCC for review. The coordinator will be notified when the clinic attains full certification.

Data Entry Certification

Each person who enters data into MTOPS Form Manager must be certified before they can enter "real" study data. Data entry personnel will be trained at the Training Session given by the BCC or by the Study Coordinator. If a person is no longer working on the study, the BCC must be notified. Data entry certification requirements are outlined as follows:

1. Data entry personnel will be trained in the study hardware. In particular, data entry persons must be familiar with the following components: CPU, video monitor, printer, and modem.
2. Data entry personnel will receive training in the study software to include familiarity with:
 - a. Menu System
 - i. Add and Update modes
 - ii. Difference between Test and Production data bases
 - b. Accessing specific forms from the menu
 - c. Browse Table
 - i. How to locate a form with a specific screening number
 - ii. How to move between the browse table screen and the form screen
 - d. Accessing and using the File and Mode Functions

3. Data entry personnel will receive training in the study forms used for data collection to become familiar with the form structure and corresponding software structure (e.g. layout, skip pattern, etc.)
4. Data entry personnel will receive training in the edit code system to understand and know how and when to use the edit codes and when to put completed study forms in a "problem" pile for correction/clarification.
5. Data entry personnel to be certified should practice entering a minimum of five (5) copies of each case report form into the computer using double data entry in order to develop familiarity with the study software prior to entering real study data.
6. A certification set of study forms will be sent from the BCC for data entry certification. Due to the randomization number scheme, only one person can be working on certification at a time. The BCC should be notified once the certification set is entered. The BCC will review the accuracy of data entry for certification. Please follow these steps for PC Certification:
 - a. Clear the test database ("Clear Test Databases" under the Options Menu).
 - b. Use the test database (Click on "Test Data").
 - c. Toggle add verifying to on (Click on "Double Data Entry On").
 - d. Enter all of the forms supplied by the BCC in chronological order. This will ensure that Form B04 for patient __101 is entered first and that for patient __102 is entered second.
 - i. When prompted "Enter Keyer Initials," the initials of the data entry personnel being certified should be entered. (The same initials must be used at all prompts.)
 - ii. Enter "CERT" as the initials for the "Form Completed By" on all forms not the initials of the data entry personnel being certified.
 - e. Extract the certification data ("Extract New Test Data" under the Options Menu). Enter the initials of the data entry personnel being certified (not "CERT"). The extract should only be performed once or all of the data will be lost.
 - f. Inform the BCC of extraction and the initials of the data entry personnel.
 - g. After notification from BCC, repeat steps a through g except step c. (leave add verifying off for single data entry).
 - h. Notify the BCC when completed and extracted.
 - i. The BCC will notify the coordinator in writing of all final PC certifications.

Data Audit Visits

Each of the clinics will be visited by the staff of the BCC, and other experts as required. At these site visits, the monitors will review procedures with the clinic coordinators/technicians, assess proficiency in executing the study protocol, review deficiencies detected in monitoring the performance of the clinics, compare the computerized master data base information with case report form documents and receive feedback on the adequacy of the centralized support operations.

Clinical Monitoring Visits

The BCC has subcontracted ACRN for the clinical monitoring. Each of the clinics will be visited three times a year by clinical research assistants (CRAs) contracted by the BCC. At these site visits, the monitors will perform a site initiation, review procedures with the clinic coordinators/technicians, review deficiencies detected in monitoring the performance of the clinics, review the drug accounting records and compare the source documentation with case report form documents. A training session will be held for the CRAs by the BCC.

The first visit (site initiation) will entail an assessment of the availability of source documents, patient binders,

and other study-related documents; the availability of laboratory facilities; the availability and proper storage of study drugs; and the accessibility and security of the microcomputer.

In subsequent years ongoing site visits will occur. On-going site visit responsibilities include a 100% eligibility review, a comparison of CRF's and source documentation, drug accounting reviews, and site visit reports. From Year 1 through 6 these visits will be conducted two or three times per clinic per year.

Performance Reports

During MTOPS, the BCC will monitor the performance of the clinics and produce periodic reports summarizing protocol performance. A major objective will be to recruit and randomize 2800 eligible MTOPS patients. The performance of the seventeen clinics in recruiting eligible MTOPS patients will be carefully monitored by the BCC. Recruitment summaries will be issued to the Steering Committee and the Recruitment/Adherence Subcommittee throughout the two year recruitment and randomization period showing the number of patients screened, number randomized, and reasons for ineligibility or patient refusal to participate by clinic. The reasons for ineligibility will be compared among the seventeen clinics, and if large differences are found, explanations for these differences will be sought. If the randomization rate falls below the desired number of patients per month (i.e., 6 to 7 per clinic per month), data concerning reasons for ineligibility and refusal will be used to try to identify strategies that would increase the randomization rate.

The BCC will prepare reports 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. The item-specific missing value rate on each case report form will also be monitored.

Other reports will consist of comparisons between the treatment groups and clinics in the characteristics of the patients who enter the trial. If differences are found among the clinics, procedures at each center will be reviewed to attempt to distinguish between differences in the patient population and differences caused by variation in the patient selection or measurement techniques.

Treatment non-compliers will not be excluded from statistical analysis, because outcomes of patients receiving sub-optimal levels of drug treatment to be important in examining overall treatment efficacy. Investigators are to encourage patients to take all of their prescribed coded medication. At each scheduled visit, patients will return all unused coded medication so that a count of returned tablets can be performed and percent compliance recorded.

The BCC will work closely with the clinics to ensure that follow-up information on primary and secondary outcomes is ascertained for all inactive patients so that an appropriate intention-to-treat analysis can be performed (see following section, Intention-to-Treat).

BIostatistical Considerations

Intention-to-Treat

All statistical analyses will be based upon the total cohort of participants randomized into the trial. Although data on some participants may be missing at points in time, all relevant data available from each participant will be employed in all analyses. In addition, all participants will be included in the randomly assigned treatment group. Group assignment will not be altered based on the participant's adherence to the assigned treatment regimen. In this way, the validity of all analyses is assured since any comparison between randomly assigned groups is unbiased. To do otherwise would require invoking untestable assumptions to provide for the validity of the resulting analyses. This "intent-to-treat" analysis philosophy has been strongly advocated by the NIH and FDA. An intent-to-treat analysis

provides the most unbiased assessment of the true therapeutic benefits of a treatment to be expected under usual clinical conditions.

Participant compliance with the assigned treatment regimen often is the most important single operational issue during randomized clinical trials. For MTOPS the primary measures of compliance with the drug treatment regimen will be based on pill counts. The degree of compliance will be continuously monitored by the clinic staff and the BCC in an attempt to achieve the treatment goals of therapy in all participants as originally randomized.

For the analyses of the trial outcomes, all participants will be included in all analyses in the randomly assigned treatment group regardless of the degree of compliance. To do otherwise could severely bias the results. Compliance is viewed as a "process variable", which should be analyzed as an outcome variable and considered in the overall interpretation of results.

Randomization Scheme

Participants will be pre-stratified with respect to clinic and will be randomized to finasteride or placebo using an adaptive biased-coin design based on a generalized Friedman's urn model (Friedman, 1949; Wei and Lachin, 1988). The first participant is assigned to either finasteride or its placebo with probability 0.5. Subsequent participants are randomized to finasteride with probability equaling the proportion so far assigned to placebo, and vice-versa. In this way, treatment assignments are progressively balanced. Participants assigned to active finasteride are then assigned to doxazosin or its placebo using a second urn process, and participants assigned to finasteride placebo are subsequently assigned to doxazosin or its placebo using a third urn process. The BCC will develop the randomization master list prior to the beginning of randomization and forward it to the drug distribution center.

Sample Size and Power

The design of MTOPS stipulates that a clinical trial lasting 6 years with 2 years of recruitment will be conducted with 17 clinics randomizing a total of 2,800 participants. This section discusses the factors which affect the sample size requirement and power of MTOPS to detect a difference between treatment groups in the cumulative incidence of progression of BPH.

Since three pairwise comparisons are planned (i.e., each of the active treatment groups vs. the placebo group), a standard Bonferroni adjustment will be used, which requires that a level of significance of $\alpha/3$ be used for each of these pairwise comparisons to guarantee a study-wise type I error of α (Miller, 1981). Since two-sided tests will be used at all times, the adjusted level of significance for each two-sided test is 0.0167 to obtain an overall 0.05 level of significance.

Sample size computation. In calculating the sample size for a clinical trial, it is necessary to specify a difference between the groups considered to be of clinical interest. For this trial, where the primary outcome analysis is based on time-to-event, the difference between two treatment groups is specified in terms of the relative hazard rate, $RHR = \tilde{\lambda}_e/\tilde{\lambda}_c$, where $\tilde{\lambda}_e$ is the progression hazard rate in the experimental group (i.e., active treatment groups, depending on the comparison desired), and $\tilde{\lambda}_c$ is the hazard rate in the control or placebo group. Assuming that time to progression is exponentially distributed, a 25 percent incidence rate over 5 years gives a control hazard rate of $\tilde{\lambda}_c = 0.058$ (i.e., $0.25 = 1 - e^{-5\tilde{\lambda}_c}$). The Steering Committee determined that a one-third reduction in the placebo treatment group progression hazard rate is of clinical interest, giving $RHR = 0.67$. The formula of Lachin and Foulkes (1986, equation 6.2) determined that the total effective sample size required to ensure 80 percent power of detecting a one-third reduction is $N = 2,445$ (612 per treatment group).

Adjustment for losses to follow-up. Lost to follow-up is defined as cessation of scheduled follow-up visits by a randomized participant prior to BPH progression or the end of the full-scale trial (i.e., 3/01). The total sample size goal must be large enough to compensate for losses to follow-up so that the total effective sample size of $N = 2,445$ is

realized. The Steering Committee determined that a reasonable estimate of losses to follow-up over the course of the trial is 5 percent per year. Hence the full-scale trial should recruit $N = 2,752$ participants (688 per treatment group) to account for eventual losses to follow-up.

Adjustment for treatment non-compliance. In some studies, the sample size computation is adjusted to account for those participants who are non-compliant with the assigned coded medication regimen. The Steering Committee decided not to incorporate this adjustment, as the trial is interested in detecting a one-third reduction in progression in a "real world" setting rather than a 33 percent pharmacologic difference. Hence, the interest is in determining the effect of medical therapy in a realistic population, where participants may be non-compliant with their medication prescription, for a variety of reasons.

Study Power. If 2,800 participants are recruited with 5 percent per year losses to follow-up, the trial will have 80 percent power to detect a one-third reduction. If the total number of participants recruited is 2,400 or 2,000, the trial will have power of 72 and 63 percent, respectively (assuming 5 percent per year lost to follow-up).

Looking alternatively at different incidence rates, which may be important due to the minimal prior information on incidence of BPH progression, a full recruitment of 2,800 participants will yield power of 87 percent if the incidence of progression in the control group over 5 years is 30 percent, 69 percent power for an incidence of 20 percent, and 54 percent power, if the incidence is 15 percent (these computations assume $RHR = 0.67$).

Analytic Methods

Multiple Comparisons. Since MTOPS consists of four independent treatment groups, multiple comparisons will be a consideration. The Bonferroni adjustment is often employed to control the overall Type I error probability for a set of m multiple comparisons, except in those minority of circumstances where less conservative multiple comparison procedures apply (e.g. ANOVA). This adjustment uses a critical p -value of α/m for m comparisons. However, less conservative closed sequentially rejective procedures have been developed by Holm (1979) and Hochberg (1988), among others. In these methods, the Bonferroni adjustment only applies to the largest observed difference among the many to be assessed, less severe adjustments apply to smaller differences. These methods will increase the power for the overall set of multiple comparisons over that provided by the ultra-conservative Bonferroni adjustment. However, since the Bonferroni adjustment would still be applied to the largest of the m comparisons, then for evaluation of study power and sample size using a single 2-group comparison, this adjustment should also be used to determine the critical value for the test statistic.

Life-Table Analyses of Time to BPH Progression. In MTOPS the principal analysis will be a lifetable analysis of the time to progression of BPH. In such an analysis, "events" are observed over time and the groups compared with respect to the cumulative incidence or "survival" (one minus cumulative incidence) functions. Separate actuarial or product-limit life-table estimated cumulative incidence curves can be calculated for the treatment groups and the curves compared using a rank test (Miller, 1981; Kalbfleisch and Prentice, 1980). A variety of rank tests have been proposed with different scoring functions, the most common of these are the logrank test and various modifications of the Wilcoxon test. The logrank test is more efficient under a Lehmann alternative (i.e., proportional hazards) whereas the Wilcoxon test, when compared with the logrank, puts more emphasis on early rather than later differences in survival (Tarone and Ware, 1977; Harrington and Fleming, 1982). Gastwirth (1985) and Zucker and Lakatos (1990) describe robust tests which are sensitive to a wider range of alternative hypotheses, including the case where there is a range of "lags" in time before treatment effects become manifest. In general, the logrank test is most widely used because it has a "relative risk" interpretation. Secondary questions addressing the equivalence of the three active drug groups are best addressed through the use of confidence intervals on the "relative risk" rather than tests of hypothesis.

Adjustment. Traditionally the principal analysis in most trials is based on an overall assessment of treatment effect within the total cohort of participants studied, unless otherwise indicated. However, the possibility that some

stratification errors may result in an unadjusted study should be considered. For example, participants with a baseline post void residual of 75 ml may not be considered in the same clinical category as participants with a post void residual of 300 ml at entry. Similarly, participants are included in the trial only if there is a maximum urinary flow rate of 15 ml/sec or less. However, a great variation in response might exist between, for example, an individual whose maximum flow rate at entry is 13 ml/sec as compared to an individual whose maximum flow rate is 6 ml/sec. These potential stratification errors should be taken care of via post-stratification adjustment methods, rather than introducing other pre-stratification factors. To obtain a stratified-adjusted estimate of the overall relative risk, as a measure of treatment effect, the stratified proportional hazards model can be used (Kalbfleisch and Prentice, 1980) perhaps with transformations or additional time effects to improve the model fit. Alternately, if the proportional hazards model does not adequately fit the data, other models such as the accelerated failure time model (Buckley and James, 1979; Wei, 1992), or the proportional odds model (McCullagh, 1984) may be applied. These analyses will be stratified by the baseline post void residual, maximum flow rate or other covariates (e.g., race/ethnicity, age). In these analyses, it will also be important to assess the homogeneity of treatment effect to determine whether the treatment group differences are quantitatively similar across the levels of baseline covariate.

Subgroup analyses or regression models which employ baseline covariates (e.g., blood pressure) can be directly interpreted because of the temporal relationship between the observation of the baseline covariate, the initiation of the randomly assigned treatment, and the observation of the outcome. This is not the case, however, for analyses in which post-randomization observations are used as covariates, such as blood pressure levels or the degree of compliance over study time. Analyses involving such "time-dependent covariates" must be carefully interpreted because the covariate itself may be affected by treatment. A thorough description of these problems in the context of analyses using the proportional hazards model are presented in Kalbfleisch and Prentice (1980).

Other Outcomes. A variety of other outcomes will be assessed over time in MTOPS. The principal method of analysis of such data will be methods for the analysis of longitudinal and repeated measures data, with an allowance for randomly and non-randomly missing data. These include analyses of the prevalence of a discrete characteristic (e.g., prevalence of a 4-point rise in AUA symptom score) at successive repeated visits over time (Lachin and Wei, 1988); multivariate rank analyses of quantitative (e.g., maximal uroflow or prostate size) or ordinal (AUA symptom score) measures over successive visits (Wei and Lachin, 1984; Lachin, 1992); regression analyses using quasi-likelihoods for generalized linear models for longitudinal data (Liang and Zeger, 1986); and random or mixed effects models for within-participant "slope" analyses over time (Laird and Ware, 1982; Jennrich and Schluchter, 1986). Many of the modeling procedures analyze differences in means under a homoscedastic model. The nonparametric techniques of Wei and Lachin (1984) allow for other types of differences (e.g., differences in tails or quantiles) over time.

Interim Analyses

During the period of recruitment and follow-up, interim statistical analyses of the study outcomes will be conducted to monitor participant safety. Such analyses are ethically mandatory and are a requirement of all NIH-sponsored clinical trials (NIH, 1979). The External Advisory Board will meet periodically to review trial results. Interim reports analyzing the primary outcome pose well-recognized statistical problems which are related to the multiplicity of statistical tests to be conducted on the accumulating set of data.

Lan-DeMets Sequential Analyses. One of the most widely used procedures for the interim analysis of a clinical trial is the "spending function" approach of Lan and DeMets (1983). Basically, this method uses a function of time to specify the rate at which the total Type I error probability is to be spent during the trial so that this quantity does not exceed the desired value α level. We propose to use the spending function corresponding to an O'Brien and Fleming (1979) boundary. With this method, 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). The information time is determined by the type of statistical test to be employed. For the analysis of the time to progression of BPH, the information time is the fraction of the total number of such events to be accrued in the entire trial. However, the total number of participants to

progress during the trial is unknown. In this situation, Lan and Lachin (1990) describe an estimate of the information time based on the fraction of total participant exposure.

All participants are to be recruited over a 2 year period, and followed for another 4-6 years (for an average duration of 5 years). We propose that interim analyses for the External Advisory Board be presented midway through recruitment on 4/96, again on 4/97, and then every 6 months thereafter. At the first interim look, if all participants are recruited uniformly over the first year, the fraction of total information accrued would be $0.5/5.0 = 0.10$. Similarly, on 4/97, the fraction of total information accrued would be $1.0/5.0 = 0.20$. Each 6 month interim analysis from then on would increase the information fraction by 0.10, culminating at 1.00 at the end of follow-up, scheduled for 4/1/2001. For interim analyses according to this schedule, where the total Type I error probability at the end of the trial is 0.0167 to allow for three pairwise multiple comparisons (i.e., $\alpha/3$), then the critical values (the "boundary") for monitoring a standard normal (Z) test statistic (two-sided) are as follows:

Interim Analysis: 1	2	3	4	5	6	7	8	9	10	
Date:	4/96	4/97	10/97	4/98	10/98	4/99	10/99	4/00	10/00	4/01
Information Time: 0.10	0.20	0.30	0.40	0.50	0.60	0.70	0.80	0.90	1.00	
Boundary:	8.0	8.0	4.67	4.01	3.57	3.24	2.99	2.79	2.62	2.48

Hence, at the first "look", if the absolute value of the Z-statistic for any of the 3 pairwise comparisons exceeds 8.0, then it could be concluded that those two groups are significantly different at $p < 0.05$. At the end of the trial, significance for any of the 3 pairwise comparisons would be based on the boundary value of 2.48 for the Z-statistic.

In the Lan-DeMets procedure, the critical value at each look principally depends only on the elapsed time (increment in information) since the last look. Thus, the critical boundary value at the end of the trial remains 2.48 if additional or fewer looks are made at any time prior to the second to last look on 10/2000. Also, there is no requirement that "looks" be equally spaced. In some clinical trials, a surprising development may lead to extra "looks" or even continuous monitoring of the data, e.g. on a weekly basis. The Lan-DeMets procedure is flexible, in that one can switch from occasional to continuous monitoring of the data (Lan, Rosenberger, and Lachin, 1993), with negligible effect on the Type I error level (Lan and DeMets, 1989). Also, the above is a projection of critical values to be obtained using the Lan and Lachin (1990) estimates of the information fractions for the logrank test. In fact, the actual average duration of exposure will be somewhat less than 5.0, adjusting for events and losses to follow-up during the trial. However, this will be built into the final calculations prior to each meeting of the External Advisory Board using the expressions in Lan and Lachin (1990).

Under this group sequential procedure, the critical value required for significance at the end of the trial for any of the 3 pairwise comparisons ($Z=2.48$) is somewhat higher than the critical Z-value employed for significance in the assessment of sample size and power (i.e., $Z=2.395$ for a significance level of 0.0167, two-sided, for each of the 3 pairwise comparisons). However, this does *not* mean that the power computations presented are over-estimates. The power computed above describes the power of a non-sequential trial with only one look at the data. If one wanted to compute the power of the group-sequential trial, one would have to compute the power allowing for 10 looks at the data with the critical values presented above. In practice, the non-sequential power is usually within 1% of the sequential power using the O'Brien-Fleming spending function. Thus, no additional adjustments to sample size are required due to the application of the proposed group-sequential analyses.

Stochastic Curtailment. Drs. Halperin and Lan developed the concept of stochastic curtailment as an alternative to sequential tests (Halperin, *et al.*, 1982; Lan, Simon and Halperin, 1983; Lan and Wittes, 1988). This approach has also been widely used for the monitoring of NIH clinical trials. Basically, this procedure projects the final level of significance, or the final level of power, to be achieved at the end of the trial based on the currently observed data and projections of the future data to be obtained. This approach has been used to monitor for the early appearance

of effectiveness (e.g., Hardy, *et al.*, 1991; DeMets, *et al.*, 1984), and it is especially useful to assess the justification for early termination of a trial due to lack of effectiveness (e.g., Lachin, *et al.*, 1992).

Procedures for Monitoring Baseline Prostate Volumes

Background.

Of the 140 prostate volumes determined during the baseline period of the MTOPS pilot study, a total of 30 randomized participants had prostate volumes < 20 cc (21.4%; 95% confidence interval, 14.6% to 28.2%) and an equal number had prostate volumes > 50 cc. This protocol amendment describes the procedure to monitor the number of participants randomized in the full-scale trial with baseline prostate volumes (total gland) < 20 cc and > 50 cc.

The goal of the "small" (< 20 cc) prostate volume monitoring procedure is to ensure that the number of participants randomized in the full-scale trial with baseline prostate volumes < 20 cc is similar to the number of baseline prostate volumes < 20 cc observed during the pilot study. If the proportion of prostate volumes < 20 cc is significantly greater than 0.25 then the recruitment procedures will be modified to decrease the proportion of prostate volumes < 20 cc. Limiting the number of "small" prostate volumes randomized in the full-scale trial will:

- (1) minimize the number of randomized participants without defined BPH (e.g., lower urinary tract symptoms)
- (2) ensure that the placebo group's clinical progression of BPH rate used in the sample size determination (i.e., 5.8% per year or 25% over 5 years) is achieved. The statistical power of the full-scale trial may be undermined if the placebo group's clinical progression rate falls below 5.8% per year.

The goal of the proposed "large" (> 50 cc) prostate volume monitoring procedure is to ensure that the number of participants randomized in the full-scale trial with baseline prostate volumes > 50 cc is similar to the number of baseline prostate volumes > 50 cc observed during the pilot study. If the proportion of prostate volumes > 50 cc is significantly less than 0.15 or significantly greater than 0.25 then the recruitment procedures will be modified to either increase the proportion of prostate volumes > 50 cc or decrease the proportion of prostate volumes > 50 cc, respectively. This monitoring procedure will ensure an appropriate number of "large" prostates for analysis of the secondary outcomes (e.g., change in AUA symptom score and maximum uroflow) in the subgroup of participants with prostate volumes > 50 cc at baseline.

Monitoring Procedure.

All participants screened for the full-scale trial 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 on the TRUS and Biopsy Information Form (P01.2) and forwarded to the Biostatistical Coordinating Center (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 Adherence ® & A) Subcommittee based on periodic reports from the BCC. At specific time points during the randomization period (i.e., after 500, 1000 and 1,500 participants are randomized), the R & A Subcommittee will review the prostate volume proportions and decide whether or not to modify the recruitment procedures to decrease the proportion of prostate volumes < 20 cc and either increase or decrease the proportion of prostate volumes > 50 cc.

The R & A Subcommittee's decision to modify the recruitment procedures is based on the 99% lower confidence limit on the proportion of prostate volumes < 20 cc and the 99% lower and upper confidence limits on the proportion of prostate volumes > 50 cc. The lower confidence limit (i.e., estimated proportion of prostates < 20 cc, or > 50 cc, minus the lower error margin) is based on the normal approximation to the binomial using the estimated proportion of prostate volumes < 20 cc ($p_{<20}$), or > 50 cc ($p_{>50}$), and the total number (n) randomized. Similarly, the upper confidence limit (i.e., estimated proportion of prostates > 50 cc plus the upper error margin) uses the estimated proportion of

prostate volumes > 50 cc ($p_{>50}$).

Total Number Randomized (n)	Proportion of Prostates < 20cc (p _{<20}) or > 50cc (p _{>50})	Lower Error Margin*	Proportion of Prostates > 50cc (p _{>50})	Upper Error Margin**
500	> 0.30	0.05	< 0.12	0.03
1,000	> 0.28	0.03	< 0.13	0.02
1,500	> 0.28	0.03	< 0.13	0.02

* $z_4 [p_{<20} \times (1-p_{<20})/n]^{1/2}$ or $z_4 [p_{>50} \times (1-p_{>50})/n]^{1/2}$ where $z_4 = 2.33$

** $z_4 [p_{>50} \times (1-p_{>50})/n]^{1/2}$ where $z_4 = 2.33$

Modification of Recruitment Procedure.

Based on the their periodic review of the "small" and "large" prostate volume proportions, the Recruitment and Adherence 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 after 500, 1,000 or 1,500 participants have been randomized (i.e., the estimated proportion of prostates < 20 cc is greater than 0.30, 0.28 or 0.28 for total number randomized of 500, 1,000 and 1,500, respectively) then the number of randomized participants with prostate volumes < 20 cc will be restricted as follows:

Each clinical 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 after 500, 1,000 or 1,500 participants have been randomized (i.e., the estimated proportion of prostates > 50 cc is greater than 0.30, 0.28 or 0.28 for total number randomized of 500, 1,000 and 1,500, respectively) then the number of randomized participants with prostate volumes > 50 cc will be restricted as follows:

Each clinical 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 after 500, 1,000 and 1,500 participants have been randomized (i.e., the estimated proportion of prostates > 50 cc is less than 0.12, 0.13 or 0.13 for total number randomized of 500, 1,000 and 1,500, respectively) then the number of randomized participants with prostate volumes > 50 cc will be enriched as follows:

Each clinical will be required to randomize at least one participant with a baseline prostate volume > 50 cc for every 5 randomized participants.

CHAPTER 10: POLICIES

PROTOCOL INTERPRETATION DURING THE TRIAL

All questions regarding interpretation of the protocol or manual of operations for the MTOPS study should be directed to the Biostatistical Coordinating Center (BCC):

The Biostatistics Center
MTOPS
The George Washington University
6110 Executive Boulevard, Suite 750
Rockville, MD 20852
Telephone: (301) 881-9260
Fax: (301) 881-3589

Grant questions should be directed to:

NIH/NIDDK/DKUHD
6707 Democracy Blvd., Room 617
Bethesda, MD 20892
Telephone: (301) 594-7717
Fax: (301) 480-3510

INFORMED CONSENT

Every patient candidate will be asked to give informed consent to participate in the study. The patient's consent is required before performing procedures called for in the pre-randomization and follow-up visits.

The Steering Committee has recognized that individual clinics may require that the Informed Consent Form be amended to include additional statements, or be re-worded to clarify existing statements. All such modifications to the Informed Consent Form must retain and should not detract from the content of the prototype Informed Consent Form (See Appendix).

The consent form must be approved by the Human Subjects Committee or any other institutional committee which has been created to guarantee the rights of patients participating in medical experimentation. In general, the written consent and the verbal explanation to the patient should include no language by which the patient is made to waive or appear to waive any legal rights or to release the institution or its agent from liability for negligence. Guidelines for protecting the rights of patients who agree to participate in medical experimentation may be found in The Institutional Guide to DHEW Policy in Protection of Human Subjects (DHEW Publication No. (NIH) 720102).

Prior to the patient's signing of any Informed Consent Form, the clinic director must read the form to the patient pausing to clarify any points which are not understood by the patient. Every patient must receive a detailed explanation of the study including a description of what is to be expected of each patient in terms of tests, follow-up visits and drug administration. All patients must understand the risks and benefits of the alternatives for the management of benign prostatic hyperplasia (observation, standard treatment or participation in the clinical trial). All patients must understand the principles of randomization. The form is to be signed only when it is clear that the patient is cognizant of all the points covered on the Informed Consent Form, and only after the patient is aware of the procedures to be applied. In all

instances, the form must be signed by both the patient and the clinic director who explained the informed consent to the patient. A copy of the signed consent form will be given to the patient.

The patient's right to refuse to sign the Informed Consent Form shall not be questioned. Signed consent to all procedures, however, is required if the patient is to be evaluated and eventually randomized into the study. Further, the patient's right to withdraw consent after signing such a form shall not be questioned. Such withdrawal prior to randomization will automatically render the patient ineligible for inclusion. In the event of withdrawal of consent after randomization, those procedures for which consent is withdrawn shall not be performed.

SHIPMENT OF DRUG SUPPLIES

Merck and Pfizer will supply sufficient quantities of coded medication (finasteride, finasteride-placebo, doxazosin and doxazosin-placebo) free of charge. (See the *Medical Therapy Protocol* in Chapter 1, 5). All coded medication will be mailed out by a central distribution center, McKessonHBOC Clinical and Biological Services. No drug will be shipped until the BCC has received the following:

- ! Form 1572 (Originally sent to NIDDK).
- ! An IRB approval form.
- ! A sample of the Informed Consent Document.
- ! The normal range values of the clinic's laboratory tests for all laboratories that will be used. If more than one laboratory will be used, contact the BCC for the Laboratory Code. Changes to these values during the study period will be updated by the clinic using a Clinic Laboratory Normal Range Report (Form R01).
- ! Successful completion of the Protocol/ Manual of Operations Quiz.

PROTOCOL CHANGES DURING THE TRIAL

Background

Prior to the initiation of MTOPS, the protocol was finalized to incorporate changes arising from suggestions of the Steering Committee, and changes arising from practical experience in pre-testing the Manual of Operations and case report forms during the pilot study.

In considering protocol changes after the trial has begun, the foremost objective will be to preserve the scientific integrity of the study and to guard patient welfare, assessed through benefits and risks. Thus, while it is desirable to minimize further protocol changes, an occasion might arise in which protocol changes are necessary for patient welfare.

Policy

Accordingly, changes affecting the scientific validity of the study shall be adopted only if they are urgently required to ensure patient welfare. Major protocol changes of this kind would necessitate stopping the original protocol and then starting again with a new protocol. Thus, for example, a change in the time or the character of the principal follow-up observations is unacceptable. Similarly, a change in the drug dosage plan is to be vigorously resisted.

Any major protocol change compromises the initial study objectives either through a reduction in the sample size or by restricting the types of statistical analyses one might perform, or both. In cases where changes are absolutely necessary, all options should be carefully considered and evaluated--both biostatistically and medically. Early termination of the study must be among the alternatives considered.

Procedures

The External Advisory Board will have the primary responsibility for recommending protocol changes based upon scientific considerations of emerging results of the study related to patient welfare (benefits and risks). Although the Clinical Review Committee, through their activities, may encounter some events related to the welfare of individual patients, only the External Advisory Board will have access to all the data. Therefore, the Clinical Review Committee will notify the Biostatistical Coordinating Center of problems they encounter and the BCC will then conduct analyses of relevant data. The results of these analyses will then be presented to the External Advisory Board either at a regularly scheduled or emergency meeting.

At each meeting, the External Advisory Board will examine all available data, especially that related to patient safety. The External Advisory Board will then decide whether any changes in the study protocol are justified, and if so, will present the recommended change to the Steering Committee, which will make the decision as to whether or not the change is to be adopted.

The Steering Committee will have the primary responsibility for recommending protocol changes which are based on operational considerations or issues other than results of analyses of safety and efficacy. In these cases, the BCC will make every attempt to reconcile the issues within the frame work of the study protocol. If such issues cannot be reconciled, the BCC will evaluate all possible options, and present the issue and the recommended protocol change to the Steering Committee. The Steering Committee will consider each recommendation and decide whether a formal change in the protocol is required. The resulting protocol change will then be presented to the External Advisory Board, and if the Board concurs, the change will be adopted.

Likewise, any further change in eligibility criteria should be carefully considered in terms of its impact on patient recruitment, and the relevance of the defined eligible population to the study objectives. A change in eligibility criteria should be adopted, however, only if the major objectives of the study are in jeopardy either due to lagging recruitment or a population which is too narrowly (or broadly) defined to be clinically relevant. If the External Advisory Board judges a clinic's recruitment performance to be below average, the Board may advise NIDDK to exclude the clinic from participation in MTOPS.

Finally, all members of the Steering Committee are encouraged to notify the Biostatistical Coordinating Center of any problems encountered or any suggested enhancements to the protocol which would improve the scientific validity of the study (e.g., a change that will enhance patient adherence without altering the basic plans of treatment observation). Along this line, changes which clarify protocol provisions or fill in gaps in the study plan are generally acceptable on the grounds of "better late than never".

PUBLICITY AND PUBLICATIONS

During the study, there will be no effort to publicize MTOPS. However, since information may be solicited by the lay or scientific press, it is desirable that all information relating to MTOPS be disseminated through the Steering Committee. Individual clinics will be allowed (but are not encouraged) to provide limited information to the press as described below. Further, since patient recruitment maybe by physician referral, clinics will be allowed to make limited presentations to the medical community.

All scientific presentations or publications derived from MTOPS will originate from the Steering Committee. Individual investigators may initiate a publication provided that approval is received from the Steering Committee. Thus, the Steering Committee will coordinate, monitor, review and possibly prepare all press releases, interviews, presentations and publications relating to MTOPS.

Press Releases and Interviews

A press release is defined as a document given to radio, television, newspapers, popular periodicals without national circulation, or scientific journals not indexed in the Index Medicus. An interview is any discussion with a member of the press, a science writer or a radio or television commentator, which in turn provides information for public dissemination. Press releases and interviews will not be initiated by clinics unless they comply with the specifications below.

If a clinic director is solicited for a press release or interview, then one may be given without prior review and approval by the Steering Committee provided that the substantive content is limited to information available either in the MTOPS Protocol or the Manual of Operations with no added interpretations or inferences. A copy of each prepared release, however, must be sent to the Biostatistical Coordinating Center. Should a clinic be solicited for information other than that detailed above, then the clinic should refer the soliciting party to the Biostatistical Coordinating Center.

Presentations and Publications

A presentation is the delivery of information to scientific, professional or public groups, such that public dissemination might ensue through publication, press releases, etc. Under these guidelines, a seminar given within a closed academic setting would not be classified as a presentation.

A presentation may be given without prior review and approval by the Steering Committee provided that it is limited to substantive information previously released by the Coordinating Centers (e.g., protocol or Manual of Operations), and does not have added interpretations or inferences. Any discussion of MTOPS that goes beyond these items of information must be approved by the Steering Committee.

A publication is any document submitted to a professional journal listed in the Index Medicus or any popular periodical with national circulation. All publications of major results of MTOPS will be prepared under the direction of the Steering Committee. Publication of results of ancillary studies by individual investigators will be allowed with approval by the Steering Committee.

Presentations and publications of MTOPS may be initiated either by individual participants or by the Steering Committee. An outline of the proposed presentation or publication will be submitted to the Publications Subcommittee for approval. Where appropriate, a participant in MTOPS will be appointed by the Publications Subcommittee to chair an ad hoc writing committee to draft each paper in a prescribed format within a stated time limit.

The primary papers submitted for publication will be under corporate authorship as "MTOPS Research Group". Within the title of each presentation and publication will be included the phrase: "MTOPS Research Group". An asterisk or other appropriate symbol following the word "Group" will be used to identify the participating investigators, co-investigators, and their institutions in a footnote. The chairman for the development of each secondary manuscript will designate the senior and co-authors.

In addition, individual investigators involved in MTOPS may request access and publishing rights to data accumulated during MTOPS provided that such action does not conflict with publications being or to be prepared by the Steering Committee. Presentations and publications may thus be prepared on behalf of a limited number of investigators and clinics. These would include the results of any approved or informal ancillary study carried out in MTOPS population, or any other work supported partially or wholly by MTOPS grant funds. All such presentations or publications must first be submitted to the Publications Subcommittee for review.

Review of Publications

Each manuscript prepared for publication will be reviewed by a member of the Steering Committee (regular or ad hoc) and a member of the External Advisory Board. The recommendation for any major modification of the manuscript

will be reviewed by two other individuals, one from each of these two committees. If the additional reviewers concur with the recommendations, the authors will modify the manuscript.

Review of Presentations

The following is the policy for review of presentations:

1. An analysis request including an analysis plan must be submitted to the BCC. The BCC staff will inform the investigator as to whether there is ample time to perform the analysis required for the Executive Committee abstract submission timeline.
2. The abstract is submitted to the Executive Committee for review 30 days prior to the abstract deadline.
3. After committee approval, submission and acceptance for poster or presentation, the final draft is submitted for review by the Publications & Presentations Subcommittee two weeks prior to the presentation.
4. A copy of the final slides or poster is sent to the BCC to be kept on file.

ANCILLARY STUDIES

An ancillary study is any study which involves documentation of clinical, serological, or pathological alterations which are consequent to the patient's therapy. It is anticipated that individual investigators may desire to perform ancillary studies (i.e., apply procedures to or conduct evaluations of MTOPS patients), in addition to those specified in the common study protocol. Such studies, however, may not interfere with the objectives of the main trial. A proposal outlining the aim of each ancillary study, procedures to be employed and preliminary data demonstrating feasibility must, therefore, be submitted to the Ancillary Studies Liaison for approval, regardless of whether additional funding is requested of the study or another source. The proposal will then be approved if the Steering Committee is satisfied that the proposed ancillary study is of scientific value and will not adversely affect the regular MTOPS treatment program. The proposal should be approximately 3 pages and comprised of: 1) a hypothesis, 2) specific aims/objectives, 3) an introduction to and the significance of the study, 4) a description of the patient population, 5) research design (including sample size), 6) methodology (including the Principal Investigator's prior experience with the techniques proposed), 7) potential areas of impact on the full-scale trial and 8) planned funding (including data analysis). A list of references is not necessary.

It is preferable that ancillary study results not be disclosed until the treatment of all patients in the full-scale trial is completed, the results appropriately analyzed, and accepted for publication. However, the Ancillary Studies Liaison may approve analysis and release of ancillary study data if it has no chance of influencing the major outcomes of the trial or leading to premature disclosure of results of the full-scale study. A written request from the ancillary study investigator or the Principal Investigator for analysis of ancillary study results would then be reviewed by the External Advisory Board. The early analysis of the ancillary study would then be evaluated on two grounds--the appropriateness of the request, and the potential effects of premature disclosure.

At the conclusion of the period of treatment of MTOPS, each ancillary study investigator will analyze his data as needed. During the study, however, each ancillary study investigator will be expected to periodically review all obtained results for each individual patient, and to report to the Biostatistical Coordinating Center any findings which may be related to the major study. The staff of the Biostatistical Coordinating Center may then request that the raw data be forwarded to the Biostatistical Coordinating Center for analyses and subsequent review by the External Advisory Board. The analyzed results, however, will be communicated back to the ancillary study investigator if it is felt that disclosure of the ancillary study results would not impair the major study.

RECRUITMENT

The first important task is to recruit and randomize the 2800 patients required to assure the statistical validity of the study. This will require that each of the clinics recruit their quota of patients during the 24 month recruitment period. The study is comprised of 17 clinics each of which must recruit 165 patients to meet this goal. This translates to approximately 6 to 7 patients per clinic every month.

If it is found that recruitment is lagging behind schedule, the Steering Committee will have two choices. First choice would be to increase the recruitment efforts of the existing clinics; and second would be to modify the entry criteria in order to allow randomization of patients who would previously have been excluded. Of the two choices, the latter is to be firmly resisted because it would entail a change in protocol as described previously.

REPORTS AND INTERIM STATISTICAL ANALYSES

During the execution of the study, four types of reports will be periodically generated by the BCC: patient recruitment, clinic performance, quality control and patient safety.

Recruitment

The purpose of these reports will be to monitor the rate of patient accrual within each clinic, and also to monitor the reasons for exclusion of patients who are evaluated for study and then found to be ineligible. During the initial period of the study, recruitment reports will be generated twice per month to monitor the rate at which recruitment is proceeding. If recruitment appears to be proceeding at the anticipated pace, the frequency of such reports may be reduced. These reports will be sent to the members of the Steering Committee and to the clinic coordinators.

Clinic Performance

The purpose of these reports is to assess protocol adherence and the quality with which the protocol is being implemented. Factors to be evaluated will include forms completion and submission, adherence to the follow-up schedule for each patient and the rate of patient dropout and withdrawal, adherence to the clinical management protocols, and submission and handling of laboratory and biopsy specimens. These reports will be generated at periodic intervals during the study. The reports will be sent to the Steering Committee.

Quality Control

To estimate the reliability of Diagnostic Center measurements of the serum and urine aliquots submitted by the clinical centers, the central laboratory staff will perform a simple replication reliability study during the trial. Results of the re-analysis of a selected sample of serum and urine aliquots will be presented to the External Advisory Board.

Patient Safety Monitoring

At periodic intervals during the period of follow-up, the External Advisory Board will meet to review the accumulated study data concerning patient safety. Statistical reports will be prepared by the BCC for review by the External Advisory Board prior to each meeting.

Each patient safety monitoring report will include tabulations and analyses of the patient characteristics by treatment group, all exits from the study by treatment group, all major clinical events by treatment group, including those that may have occurred after a patient had reached a stop-point, and frequency of entry to and exit from clinical management protocols by treatment group.

In reviewing each patient safety monitoring report, the External Advisory Board will assess the need to perform an in depth evaluation of the benefits and risks of continuing the study based on the accumulated data to that point in time. If it is determined that patient safety would be compromised by continuation of this study, or if it is determined that the study objectives have been satisfied based on the data accrued to date, the committee may vote to terminate

the recruitment and follow-up of patients before the end of the study. The External Advisory Board may also recommend modifications of the protocol based on concerns for patient welfare or the scientific integrity of the study.

Because this is a multi-center clinical trial, no one clinic investigator or staff will be aware of the combined patient experience during the study. Each clinic should therefore interpret a decision by the External Advisory Board to continue the trial as indicating that there is no discernible risk to patient safety, nor has therapeutic benefit of Medical Therapy been demonstrated.

These interim analyses for patient safety will pose recognized statistical problems related to the repeated analysis of accumulated data. In this context, the usual significance level or p-value will be misleading because the chance of a false-positive result increases with each successive analysis of the data. Thus, any decision by the to terminate or modify the protocol would be based on appropriate statistical analyses which would control for the effects of repeated examinations of the data.

CLASSIFICATION OF OUTCOME EVENTS

Termination of therapy prior to the end of the follow-up period will be considered an outcome event. The classification of outcomes will be conducted along the following lines.

Clinical Events:

Patients who reach an outcome as represented by a major clinical event related to BPH or death will be so classified.

Non-Compliant:

These are patients who are forced to terminate their therapy due to clinical events which are not related to worsening of their BPH symptoms or effects of the therapies employed.

Inactive Follow-up:

This includes all patients who cease participation of the scheduled follow-up visits for reasons other than death.

The medical history of each patient who reaches an outcome event will be reviewed by the Clinical Review Committee to determine that the termination of therapy was in fact clinically appropriate, and to provide the final classification of each patient for purposes of statistical analysis.

All patients will continue to be followed to the extent possible until the administrative censoring date or death regardless of the occurrence of the outcome events. After termination of therapy, all subsequent statistical outcomes will be reported and reviewed by the Clinical Review Committee.

CHAPTER 11: CASE REPORT FORMS

GENERAL INSTRUCTIONS

All Case Report Forms **must** be legibly completed in ink. No white out or pencils may be used, clearly mark the boxes when placing an "X". Corrections should be made in red ink by neatly drawing a line through the incorrect response, writing the correct answer, and initialing and dating the change. If there is no information gathered for a particular form, then that form should not be completed at all (not even the identification section). **Note:** if it is not necessary to complete a particular section of a Case Report Form, the section should be left blank. Under no circumstances should a line be drawn through a section of a Case Report Form. If a Case Report Form is deleted, a big red 'X' should be drawn on the first page and a short description should include the reason why the Case Report Form was deleted. Coordinator should initial and date the deletion.

Ordering Supplies from the BCC

Procedure for Ordering Forms

1. The BCC will provide forms and binders. The coordinator should complete the *Requisition Form* in the Appendix and FAX it to the BCC. Please be sure that you are using the most recent version of the form.
2. Allow 2 weeks for the BCC to ship out the requested supplies/forms.
3. When the order is sent by the BCC, a *Confirmation Form* will be faxed to the clinic stating what was sent, how it was sent (ex. UPS, regular mail, etc) and how many boxes were sent.
4. When the packages are received, the coordinator must verify which supplies were received and sign the *Confirmation Form* and FAX it back to the BCC.

Other Notes on Ordering Supplies

1. Binders (except for additional binders for a patient) should be ordered in multiples of 12.
2. Additional year packets are sent periodically for active patients randomized. If a packet is needed for an inactive patient who has reactivated, the patient number should be included on the order form.
3. The bottom portion of the *Requisition Form* should be completed when ordering individual forms that are not contained in the packages or additional forms. Specify the form, the number of copies requested, and indicate, where appropriate, if Spanish or interview versions are needed.

Instructions for Completing Patient Identification - Section A

The following instructions are to be used when completing the Patient Identification section (Section A) of any case report form. Not all of the information listed below is required on every form. If a patient has been randomized at the time of the visit, clinic number should be recorded and a patient label affixed to the Case Report Form over the patient number, initials and date of birth fields. Patient labels ensure accurate recording of information and also aid in identifying AUA symptom score and creatinine rises.

Clinic Number

Record the corresponding clinic number in the boxes provided, as per the following list. The clinic number is

provided in the MTOPS Directory of Participants.

Patient Identification Number

Complete ONLY Screening Number **OR** Patient Number

Screening Number (If before randomization, Screening number)

Record the patient's screening number in the boxes provided (beginning with **S** followed by 4 digits). At the first screening visit, the patient will be assigned a screening number. The screening number always begins with a "S" and the clinic's coordinator assigns the numerical portion, preferably in sequence. Leave no blank boxes.

Patient Number (If after randomization, Patient number)

Record the patient number. The patient number is assigned at randomization by the computer. The first two digits will be the clinic number and the last three will be a patient specific number. Leave no blank boxes.

Patient's Initials

Record the first two letters of the patient's first name and the first two letters of their last name, regardless if there is another patient at the clinic with the same initials. Leave no blank boxes. It is very important to always use the same initials for each patient, i.e. someone named James (JA) and called Jim (JI) would have different initials. Except for Form B02, when entering data into the microcomputer, this field will be automatically inserted by the microcomputer. The initials should be verified by the data entry person.

Patient's Date of Birth

Record the patient's date of birth in the boxes provided. Except for Form B02, when entering data into the microcomputer, this field will be automatically inserted by the microcomputer. The date of birth should be verified by the data entry person.

Instructions for Completing Conclusion Box

The following instructions are to be used when completing the box at the end of each form. In some cases, the box is located on the first page instead of at the end of the form, for example, the patient questionnaires. This box MUST be completed.

Initials of person completing form

The person completing the form should record the first two letters of their first name and the first two letters of their last name, leaving no blank boxes. It is very important to always use the same initials for each staff member, i.e. someone named Elizabeth (EL) and called Beth (BE) would have different initials.

Form entered in computer?

When the form has been entered in the computer, the person who entered the data should check the box.

P.I. Signature and Date

If the space is present on the form, the Principal Investigator should sign and date the form. The P.I. must sign off on one form for each visit and all event reports.

Instructions for Completing the Information at the Top of Each Page

Remember to complete the fields at the top of each page of each form. This information is important for quality control, in case the pages of a form get separated or for identification if only one page is used in communicating information.

INSTRUCTIONS FOR COMPLETING FORM B01 - ELIGIBILITY AND EXCLUSION INVENTORY

This form should be completed during the baseline period (i.e., the patient must attend at least the first screening visit). Some questions on this form may not be answered until the Randomization Visit.

Much of this information may be obtained by conducting an interview (in person or over the telephone) or by reviewing the patient's chart. It is important to review the chart for medical history, taking particular care to perform a thorough urologic history.

Form B01, B02 and T02 must be completed for all patients who attend at least one screening visit. These three forms must be completed for **every** screening attempt. These are the only forms which are required for each patient screened. However, if any other forms were completed, then they should also be entered into the microcomputer.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of Screening Visit 1

Record the date of the first screening visit. This date must be the same date as the date in Question B.1 on Form B02 (Screening Visit 1 Inventory).

Section C - INCLUSION CRITERIA

C.1 The patient has voluntarily signed the informed consent agreement prior to the performance of any study procedures.

Record YES if the patient has signed the Informed Consent Agreement.

C.2 The patient is a male at least 50 years of age.

Record YES if the patient is male and is 50 years old or older as of Screening Visit 1.

There is no upper age limit. The patient can be excluded for cause or, if in the opinion of the principal investigator, the patient has a low likelihood of survival until the end of the trial.

C.3 The patient's 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.

Record YES if the patient's urinary flow rate is within the range 4 - 15 ml/sec at both Screening Visits 1 and 2. Refer to Form B02 (Screening Visit 1 Inventory), question I.4 and Form B03 (Screening Visit 2 Inventory), question E.4.

AND

If the patient's voided volume is greater than or equal to 125 ml at both Screening Visits 1 and 2. Refer to Form B02 (Screening Visit 1 Inventory), question I.6 and Form B03 (Screening Visit 2 Inventory), question E.6.

C.4 The AUA symptom severity score is at least 8, and less than or equal to 30.

Record YES if the patient's AUA Symptom Score is greater than or equal to 8 points, but not more than 30 points at both Screening Visits 1 and 2. All questions on the AUA Symptom Score must be answered. Refer to Form Q01 (AUA Symptom Score Questionnaire), bottom of page 2.

If all items in Section C (C.1-C.4) are answered YES, the patient is eligible to be randomized. If any item in Section C is answered

NO, the patient cannot be randomized.

Section D - EXCLUSION CRITERIA

Be sure that all correspondences pertaining to eligibility are documented in the patient's source document (medical record).

D.1 The patient has had any prior intervention for BPH (either medical or surgical).

Procedures such as a prior TURP, TUIP or BDP would make the patient ineligible.

D.2 The patient has received any prior experimental intervention for prostate disease (either medical or surgical) or is presently enrolled in any other study protocol.

If the patient has received any experimental intervention trial for prostate disease, whether it is medical or surgical, the patient is not eligible to participate in this trial.

If the patient is presently enrolled in any other experimental trial, the patient is not eligible to participate in this trial, regardless of the nature of the conflicting trial. This information can be found by looking for a copy of the informed consent in the medical record or source document.

D.3 The patient has had a previous hypersensitivity, idiosyncrasy, or clinically suspended drug reaction to alpha-blockers, quinazoline compounds, or finasteride.

It is important to screen for concomitant medications which would make the patient ineligible for the trial. If in doubt of any medication which may be exclusionary, please refer to a PDR or refer to the *Exclusionary Medications* section, in Chapter 6, page 3.

D.4 The patient has taken an alpha-1 blocker within one year of randomization.

It is important to screen for concomitant medications which would make the patient ineligible for the trial. If in doubt of any medication which may be exclusionary, please refer to a PDR or refer to the *Exclusionary Medications* section, in Chapter 6, page 3.

D.5 The patient has 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)].

It is important to screen for concomitant medications which would make the patient ineligible for the trial. If in doubt of any medication which may be exclusionary, please refer to a PDR or refer to the *Exclusionary Medications* section, in Chapter 6, page 3.

D.6 The patient has taken an estrogen, androgen, or a drug producing androgen suppression, or anabolic steroids.

It is important to screen for concomitant medications which would make the patient ineligible for the trial. If in doubt of any medication which may be exclusionary, please refer to a PDR or refer to the *Exclusionary Medications* section, in Chapter 6, page 3.

If a patient has or is taking prescription tagamet, he can be screened after a 3 month washout period. If a patient has or is taking over-the-counter tagamet on an infrequent basis, he can be randomized at the discretion of the principal investigator provided that the patient is instructed to take a substitute (such as Pepcid).

D.7 The patient has an inability to urinate.

If the patient has the inability to urinate (indwelling foley catheter or suprapubic tube), the patient is not eligible for this trial.

D.8 The patient has a supine blood pressure of less than 90 mm Hg systolic or 70 mmHg diastolic.

Record YES if at any of the baseline visits, the supine blood pressure is less than 90/70 mmHg. Please refer to Form B02 (Screening Visit 1 Inventory), question F.1.a; Form B03 (Screening Visit 2 Inventory), question C.1.a; and Form B04 (Randomization Information), question E.1.a.

Record NO if all of the aforementioned blood pressure readings are >90/70 mmHg.

NOTE: THIS REQUIRES THAT THE SUPINE SYSTOLIC BLOOD PRESSURE MUST BE \geq 90 mmHg AND THE SUPINE DIASTOLIC BLOOD PRESSURE MUST BE \geq 70 mmHg.

D.9 The patient has clinically significant renal or hepatic impairment (i.e. creatinine greater than 2.0 mg/dL or ALT (SGPT) greater than 1.5 times the upper limit of normal).

Review renal function tests (creatinine) and liver function tests (ALT/SGPT) for exclusionary values (creatinine greater than 2.0 mg/dL, ALT (SGPT) greater than 1.5 times the upper limit or normal). If any of these values are borderline for exclusion it is helpful to explain to the patient that there is a chance that he will not qualify for study participation based on these laboratory values.

At Screening Visit 1, these tests will be repeated and eligibility is determined by these values. Refer to Form B02 (Screening Visit 1 Inventory), questions M.7 and M.11.

D.10 The patient has a serum prostate specific antigen (PSA) level greater than 10 ng/ml.

Refer to the PSA value received from the Diagnostic Center on Form B04 (Randomization Information), question D.1.a.

D.11 The patient requires the daily use of a pad or device for incontinence.

Review the urologic history for incontinence (use of a daily pad or device). Since this may not always be documented, be sure to question the patient during the initial interview.

D.12 The patient has had an episode of unstable angina pectoris, a myocardial infarction, transient ischemic attack, or a cerebrovascular accident within the past six months.

Review the chart for a history of myocardial infarction, transient ischemic attack, or cerebrovascular accident within the past six months. If patient has a prescription for Nitroglycerin SL, it is important to interview the patient to ascertain the stability of the patient's angina. When interviewing the patient in regard to a cardiac history, be sure to use lay terminology (i.e. "heart attack").

D.13 The patient has 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 hypotension.

A history of dizziness/lightheadedness/fainting would eliminate the patient from study participation. Often, a patient had an episode of dizziness on one occasion for which a direct etiology was found (i.e. new glasses, dehydration). For this part of the exclusion criteria, it is helpful to contact the patient and do an interview regarding the cause of the dizziness or lightheadedness. If it is your judgement that the patient's dizziness was caused by a well-defined and self-limited entity, document this in the chart, and call the BCC to obtain approval of this patient's eligibility.

In order for a patient to be eligible for the study, he must be free of orthostatic hypotension at all pre-

randomization visits. Refer to Form B02 (Screening Visit 1 Inventory), question G.1; Form B03 (Screening Visit 2 Inventory), question D.1; and Form B04 (Randomization Information), question F.1. Record YES if any of these questions are answered YES. Record NO if all of these questions are answered NO.

D.14 The patient has a 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.

Look for a history of bladder cancer, pelvic radiation/surgery, or urethral strictures which makes the patient ineligible.

A history of sexually transmitted diseases such as gonorrhea should heighten your suspicion for a urethral stricture. In these patients, it is suggested a cystoscopy be performed to rule out stricture disease vs. BPH.

Prostate surgery of any kind or surgery for bladder neck obstruction makes the patient ineligible. A history of prostate cancer makes the patient ineligible. If the patient has a suspicious feeling prostate on digital rectal exam, but the prostate needle biopsy is negative, and the PSA is less than 10 ng/ml, the patient may be eligible for the trial.

A patient diagnosed with Prostatic Intraepithelial Neoplasia (PIN) grade I or low grade PIN is eligible for the trial. However, patients with grades II or III or high grade PIN are not eligible for the trial.

Although surgery for bladder neck obstruction is an exclusion, diagnosis of bladder neck obstruction is not an exclusion.

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

An active urinary tract disease, a cystoscopy, or a prostate biopsy within the past one month of Screening Visit 1 or an imminent need for surgery will render the patient ineligible for the study.

D.16 The patient has known primary neurologic conditions such as multiple sclerosis or Parkinson's disease or other neurological diseases known to affect bladder function.

Review the chart for such conditions such as Parkinson's disease and Multiple Sclerosis which are exclusionary. If you are conducting telephone pre-screening, this information can be obtained over the telephone.

D.17 The patient has had documented bacterial prostatitis within the past year.

Review the chart (including laboratory reports) for documented bacterial prostatitis. If the patient has a history of chronic, recurrent, non-bacterial prostatitis or bacterial prostatitis that was not documented, then the patient may still be eligible.

D.18 The patient has had two documented urinary tract infections of any type in the past year.

Review the chart (including laboratory reports) for documented urinary tract infections (2 in the past year). A patient with a history of burning on urination, but no documented urinary tract infection is eligible, however it is recommended that a urine culture and sensitivity be obtained on these patients.

D.19 The patient has a severe bleeding disorder which makes a biopsy impossible.

Review the patient's medical record and laboratory records for any indication of a bleeding disorder. This information can also be obtained by a telephone pre-screen interview.

D.20 The patient has had cancer which is not considered cured (except basal cell or squamous cell carcinoma

of the skin). A patient is considered cured if there has been no evidence of cancer within five years of randomization.

A patient with a history of cancer (other than basal cell or squamous cell carcinoma of the skin) is eligible if the cancer is considered cured, and the patient is 5 years post initial diagnoses.

D.21 The patient has any serious medical condition likely to impede successful completion of the long-term study.

Any serious medical condition that is likely to impede successful completion of the long-term study will make the patient ineligible. Some examples of illnesses that may make them ineligible include HIV, IDDM, Alzheimer's, and stroke.

D.22 The patient has a diagnosis of a thought disorder (i.e. schizophrenia, bipolar disorder).

Patients with thought disorders are not considered study candidates (i.e. patients with schizophrenia). The rationale behind this is two-fold, mainly these patients may have a problem with protocol compliance, and in addition, the question of competency arises when obtaining informed consent. A patient's mental state is often a grey area in clinical trials. Many patients may have documented depression, but each case in different (some patients may be on medication). When in doubt, use clinical judgement and keep in mind that the issues are study compliance and the patient's competency when obtaining informed consent.

D.23 The patient has a history of alcoholism or any other substance abuse which, in the opinion of the investigator, would affect compliance with the protocol.

A history of alcoholism or other substance abuse will exclude the patient from study participation. If the patient has been in rehabilitation for a reasonable period of time, and the patient has demonstrated that he can be compliant (i.e. keeps appointments), the patient may be entered in the trial. Be sure to document your clinical judgement in the source document.

If all questions in Section C (C.1-C.4) are answered YES, AND all questions in Section D (D.1-D.23) are answered NO, the patient is eligible to be randomized.

Section E - CONCLUSION

E.1 Are all questions in Section C answered YES?

Review Section C, record YES if all questions in Section C (C.1 - C.4) are answered YES. Record NO if ANY of these questions is answered NO.

E.2 Are all questions in Section D answered NO?

Review Section D record YES if all questions in Section D (D.1 - D.23) are answered NO. Record NO if ANY question is answered YES.

E.3 Will the patient be randomized?

Record YES if the patient attends the Randomization Visit and is randomized. If either question E.1 or E.2 is answered NO, the patient cannot be randomized.

If the patient will NOT be randomized for a reason that is not documented in Section C or D, complete question E.3.a.

E.3.a If no and the reason is not specified in Section C or D, specify below.

Briefly record the reason why the patient will not be randomized if it is a reason other than those listed in Section C and D.

Important Note: WHEN IN DOUBT, CALL THE BCC TO VERIFY ELIGIBILITY!

INSTRUCTIONS FOR COMPLETING FORM B02 - SCREENING VISIT 1 INVENTORY

This form and Forms B01 and T02 must be completed for all patients who attend a first Screening Visit, this means that Forms B01 and T02 must be completed for each Form B02 that is completed. These three forms must be completed for **every** screening attempt.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of Visit

Record the date the patient was seen for the first screening visit. This should be the same date as the date in question B.1 on Form B01 (Eligibility and Exclusion Inventory).

Section C - GENERAL INFORMATION

C.1 Race

Record an 'X' in the box that corresponds to the race the patient considers to be his primary race.

C.2 Marital Status

Record an 'X' in the box that corresponds to the marital status the patient considers himself at the time of Screening Visit 1.

C.3 Grade level last completed

Record '00' if the patient had no schooling or completed kindergarten
'01' - '12' for grade 1 through 12 last completed
'13' for 1 year of college completed
'14' for 2 years of college completed
'15' for 3 years of college completed
'16' for 4 years of college or an undergraduate degree completed
'17' for any post-undergraduate schooling.

Section D - MEDICAL HISTORY

At a minimum, the history consists of the items listed on the case report form. Particular attention should be directed to items in the medical history which prove exclusionary to entry on the study protocol. These exclusionary items are reiterated below.

D.1 Congenital Disease

D.2 Lung Disease

D.3 Heart Disease

A history of unstable angina pectoris, a myocardial infarction, transient ischemic attack, or a cerebrovascular accident within the past six months excludes the patient from the study. See Form B01 (Eligibility and Exclusion Inventory), question D.12.

D.4 Hypertension

The patient may not have taken alpha-1 antagonists within a year of randomization. See Form B01 (Eligibility and Exclusion Inventory), question D.4.

D.5 Renal Disease

Serum creatinine must be less than 2.0 mg/dL. See Form B01 (Eligibility and Exclusion Inventory), question D.9.

D.6 Rheumatologic/Collagen or Vascular Disease

D.7 Diabetes Mellitus

D.8 Endocrinopathy (other than diabetes)

D.9 Liver Disease

Significant hepatic Impairment (i.e., ALT > 1.5 upper limit of normal) excludes the patient from the study. See Form B01 (Eligibility and Exclusion Inventory), question D.5.

D.10 Gastro-intestinal Tract Disease

D.11 Skin Disease

D.12 Organic CNS disease

If the patient has primary neurologic conditions that are known to effect bladder function, he is excluded from the study. If the patient has a diagnosis of a thought disorder (i.e., schizophrenia, bipolar disorder) he is excluded from the study. If the patient is unable to understand the directions of the study and is therefore unable to give informed consent, he is excluded from the study.

D.13 Neoplastic Disease

D.14 Anemia

D.15 Hematologic Disease (other than anemia)

D.16 History of urinary tract infections

By history, a physician needs to have told the patient he had a urinary tract infection after an examination of the patient's urine, and has administered a course of antibiotics. A course of antibiotics administered for suggestive symptoms alone does not qualify. By chart review, sufficient documentation of a UTI involves at least three of the following: suggestive symptoms, pyuria, a urine culture with greater than ten to the fifth power colonies per cubic milliliter, or the administration of a course of antibiotics by a physician. If the patient has had two documented urinary tract infections within the year prior to the screening visit, he is excluded from the study. See Form B01 (Eligibility and Exclusion Inventory), question D.18.

If the patient has had documented bacterial prostatitis within the past year, he is excluded from the study. See Form B01 (Eligibility and Exclusion Inventory), question D.17. A history of prostatitis without culture documentation does not exclude the patient.

D.17 History of Urinary Retention

Acute retention occurs when a patient cannot void more than a few drops despite multiple attempts, and passage of catheter is then required. If there is not more than 100 cc in the bladder at the time of catheterization, then the patient does not meet the definition of urinary retention. Similarly, when a catheter is passed after a patient does successfully void, and documents a large post-void residual, implying incomplete emptying, the patient is excluded from the study. Patients who have a history of one episode of retention in the past are not excluded if they are not in urinary retention at the time of the screening visit.

D.18 Prior episode of Gross Hematuria

Gross hematuria is defined as hematuria heavy enough to be obvious to the patient or physician, unless a urinalysis reveals the color is not due to blood (as can be seen after the ingestion of beets).

D.19 History of Microscopic Hematuria

Microscopic hematuria will be defined as greater than five red blood cells per high power field on urinalysis. Microscopic hematuria does not exclude patients from the study.

D.20 Prior Biopsy of Prostate

If the patient had a biopsy within 1 month prior to the first screening visit, he is not eligible for the study at this time. The patient may be randomized after it has been more than 1 month post-biopsy.

D.21 Family History of BPH

Record YES, if there is a family history of benign prostatic hyperplasia. Record UNKNOWN if the family history is not known.

If Question D.21 is answered YES, complete question D.21.a.

D.21.a Check all appropriate relatives.

If the patient knows that there is a family history, but is unsure which relative(s) was diagnosed with BPH, check "Unknown."

If Question D.22 is answered YES, complete question D.22.a.

D.22 Family History of Prostate Cancer

Record YES if there is a family history of prostate carcinoma. Record UNKNOWN if the family history is not known.

If Question D.22 is answered YES, complete question D.22.a.

D.22.a Check all appropriate relatives.

If the patient is unsure which relative(s) were diagnosed with prostate cancer, check "Unknown."

D.23 Vasectomy

Record YES if the patient has had a bilateral vasectomy.

If Question D.23 is answered YES, complete question D.23.a.

D.23.a Year of Vasectomy

Record the year of the vasectomy according to medical records or to the patient's best recollection (e.g. if the vasectomy was performed in 1990, then record 90). Only two boxes are provided for the year, it is assumed that the year is "19__".

Section E - BPH SYMPTOMS

E.1 Duration of Symptoms

Instruct the patient to think back over the past or check his medical record and determine when his symptoms began; then record the appropriate number of years.

E.2 Stability of Symptoms during the past year

Instruct the patient to think back over the past year and determine whether his symptoms have improved, remained the same, or worsened; then record an 'X' in the appropriate box.

E.3 Has Patient seen a Urologist within the past 5 years about BPH Symptoms

Record YES if the patient has seen a urologist within the past 5 years for BPH symptoms.

If Question E.3 is answered YES, complete question E.3.a.

E.3.a What was their recommendation?

Record an 'X' in the appropriate box for the urologist's recommendation for the patient (i.e., surgery, medication, or watchful-waiting).

Section F - BLOOD PRESSURE READINGS

Refer to the *Blood Pressure Management Protocol* section in Chapter 6, page 1 for any questions regarding blood pressure.

F.1 Supine Blood Pressure (after patient is lying for 5 minutes)

F.1.a Blood Pressure

If question F.1.a <90/70 mmHg, the patient is excluded from the study. See Form B01 (Eligibility and Exclusion Inventory), question D.8.

F.1.b Heart Rate

F.2 Standing Blood Pressure (immediately upon standing)

F.2.a Blood Pressure Reading 1

F.2.b Heart Rate 1

After waiting 2 minutes

F.2.c Blood Pressure Reading 2

F.2.d Heart Rate 2

Section G - ORTHOSTATIC HYPOTENSION

Refer to the *Orthostatic Hypotension* section in Chapter 6, page 2 for any questions.

G.1 Did the patient have Orthostatic Hypotension?

If either standing systolic (question F.2.a or F.2.c) is 20 mmHg less than the supine systolic (question F.1.a)

OR if either standing diastolic (question F.2.a or F.2.c) is 10 mmHg less than the supine diastolic (question F.1.a)

OR if the patient has developed significant postural hypotension, record YES.

If this question is answered YES, the patient is ineligible for the study. See Form B01 (Eligibility and Exclusion Inventory), question D.13.

Section H - PHYSICAL EXAMINATION

The physician will document the examinations in the source document. A photocopy of the page of the case report form will help to serve as a guideline while the physician is conducting the exam.

H.1 Height

Record the patient's height in inches. Height should be obtained without shoes.

H.2 Weight

Record the patient's weight in pounds (lbs.). Weight should be obtained in lightweight clothing without shoes.

H.3 Examinations

The eight systems of the body will be reviewed by the physician, who will check either normal or abnormal. An abnormal recording should be accompanied by a comment on the line provided.

- H.3.a Head, Ears, Nose, Throat**
- H.3.b Eyes**
- H.3.c Neck (include bruits)**
- H.3.d Heart**
- H.3.e Lungs and respiration**
- H.3.f Abdomen (include bruits)**
- H.3.g Liver**
- H.3.h Skin**
- H.3.i Neurological**
- H.3.j Urogenital**

H.4 Rectal Examination

NOTE: SERUM FOR PSA MUST BE DRAWN BEFORE THE RECTAL EXAM.

H.4.a Prostate size

During the digital rectal exam, the physician must estimate the prostate size in grams.

For the rest of the rectal examination, record YES or NO. YES responses will require further explanation in the source document.

- H.4.b Nodules or indurations**
- H.4.c Asymmetry**
- H.4.d Suspicious for cancer**
- H.4.e Tenderness**

Section I - UROFLOW MEASUREMENTS

Have patient come for his visit with a full bladder. Instruct him to urinate into the white funnel. The machine will automatically begin recording at the initiation of flow and terminate at the end of micturition. (**Note:** this test should be performed when the patient has a normal desire to void and in conditions suitable for privacy.) Essentially, all the patient must do is urinate into the flowmeter while standing. Tell the patient no discomfort is associated with this test and the duration is several seconds. The Maximum Flow Rate must be equal to two seconds (i.e., 2 dots along the bottom of the uroflow strip). **Voided volume must be at least 125 ml for the test to be valid**

The information required for the case report form follows the uroflow strip in the order of information on the printout (items #1-6). Only the post void residual (item #7) must be obtained from the bladder scan printout. Transcribe the uroflow results onto the case report form, making sure that units of measurement are the same. Be certain to right-justify all numbers. The same applies to the post void residual - check units of measurement, right-justify, etc.

If the bladder scan machine in use provides a printout, this must also be maintained. If there is no printout from the bladder scan, a notation of the PVR must be made in the source document.

Mark the date and patient number (screening or study number) on each uroflow printout. Make two copies of all

printouts. One copy is to be maintained in the source document. The other copy along with the original printout is placed in the envelope in the patient's binder.

See the *Uroflowmetry Procedure* section in Chapter 7, page 1 for any questions regarding this procedure.

I.1 Voiding Time

I.2 Flow Time

I.3 Time to Maximum Flow

I.4 Maximum Flow Rate

If this value is <4.0 or >15.0 ml/sec, the patient is ineligible for the study. See Form B01 (Eligibility and Exclusion Inventory), question C.3.

I.5 Mean Flow Rate

I.6 Voided Volume

If this value is <125 ml, the patient is ineligible for the study. See Form B01 (Eligibility and Exclusion Inventory), question C.3.

I.7 Post Void Residual

Section J - CONCOMITANT MEDICATIONS

J.1 Is the patient taking any medication on a regular basis?

Record YES if the patient is taking any medications regularly.

If question J.1 is answered YES, complete J.1.a-j

J.1.a-j Record here all medications taken on a regular basis. Remember this is a "snap-shot" of medications; just record the medications being taken today (NOT all medications taken since last visit). Refer to *Exclusionary Medication* section in Chapter 6, page 3 for medications that would render the patient ineligible.

Refer to the Concomitant Medication Dictionary for the proper recording of names of concomitant medications.

Section K - PSA SERUM SPECIMEN

Refer to the *Serum Collection for PSA and Hormones* section in Chapter 7, page 3 for any questions regarding specimen collection.

K.1 Was a serum specimen collected for PSA (and hormones for biopsy patients) during Screening Visit 1?

Record YES if the serum was collected for PSA and hormones.

If this question is answered NO, the patient is ineligible for the study. See Form B01 (Eligibility and Exclusion Inventory), question D.10.

If Question K.1 is answered YES, complete question K.1.a.

K.1.a Date sent to the Diagnostic Center

Record the date the serum specimen was sent to the Diagnostic Center. This may not necessarily be the same date it was collected.

Section L - COMPLETE BLOOD COUNT

Record the laboratory results, taking care to convert the value to the units on the case report form when necessary. Refer to *Serum Collection for Hematology and Chemistries* section in Chapter 7, page 4 for any questions regarding serum collection.

L.1 Leucocyte Count (WBC)

Record the value in $10^3/\text{ul}$.

L.2 Erythrocyte Count (RBC)

Record the value in $10^6/\text{ul}$.

L.3 Hemoglobin

Record the value in g/dl.

L.4 Hematocrit

Record the value as a percentage (%).

L.5 Platelet Count

Record the value in $10^3/\text{ul}$.

Section M - SERUM CHEMISTRIES

Record the laboratory results, taking care to convert the value to the units on the case report form when necessary. Refer to *Serum Collection for Hematology and Chemistries* section in Chapter 7, page 4 for any questions regarding serum collection.

M.1 Sodium

Record the value in mmol/L.

M.2 Potassium

Record the value in mmol/L.

M.3 Chloride

Record the value in mmol/L.

M.4 Bicarbonate

Record the value in mEq/L.

M.5 Glucose

Record the value in mg/dl.

M.6 Urea Nitrogen

Record the value in mg/dl.

M.7 Creatinine

Record the value in mg/dl.

If this value is >2.0 mg/dl, the patient is excluded from the study. See Form B01 (Eligibility and Exclusion Inventory), question D.9.

M.8 Uric Acid

Record the value in mg/dl.

M.9 Calcium

Record the value in mg/dl.

M.10 Phosphorus

Record the value in mg/dl.

M.11 ALT (SGPT)

Record the value in U/L.

If this value is >1.5 times the upper limit of normal, the patient is excluded from the study. See Form B01 (Eligibility and Exclusion Inventory), question D.9.

M.12 Alkaline Phosphatase

Record the value in U/L.

M.13 Total Bilirubin

Record the value in mg/dl.

M.14 Total Protein

Record the value in g/dl.

M.15 Albumin

Record the value in g/dl.

M.16 Cholesterol

Record the value in mg/dl.

Section N - URINALYSIS

Refer to *Urinalysis Protocol* section in Chapter 7, page 4 for any questions regarding urinalysis.

N.1 Dipstick

Compare the reagent areas on the dipstick with the corresponding color chart on the bottle. Record the following dipstick readings.

N.1.a pH

For the remaining dipstick readings (N.1.b-f), record an 'X' in the appropriate box: 0, trace, 1+, 2+, 3+, 4+.

N.1.b Glucose

N.1.c Blood

If the result here is >0, be sure to complete Section N.2 (microscopic urinalysis).

N.1.d Ketones

N.1.e Protein

N.1.f Leucocyte Esterase

If this result is >0, be sure to complete Section N.2 (microscopic urinalysis).

N.2 If the dipstick is positive (greater than 0) for blood or leucocyte esterase, please send specimen for microscopic urinalysis. Please use the following table to code the results of the microscopic urinalysis.

1	None, Negative, WNL
2	1-5, Trace, Present, Slight, Rare, Occ
3	6-15, Moderate
4	16-30, Many, Frequent
5	> 30, Innumerable, TNTC

N.2.a WBC

N.2.b RBC

N.2.c Epithelial Cells

N.2.d Mucous

N.2.e Bacteria

N.2.f Casts - Hyaline

N.2.g Casts - Other

INSTRUCTIONS FOR COMPLETING FORM B03 - SCREENING VISIT 2 INVENTORY

This form should be completed if the patient is still eligible, willing to participate in the study after Screening Visit 1, and attends Screening Visit 2. At this visit, please observe the following guidelines if the patient is participating in the biopsy substudy:

1. Form B03 (Screening Visit 2 Inventory) including uroflow, Form Q01 (AUA Symptom Questionnaire) and Form Q03 (Health Survey Questionnaire) must be performed **BEFORE** TRUS and Biopsy are performed.
2. Placebo Run-in and Form B05 must be initiated **AFTER** TRUS and Biopsy are performed.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of visit

Record the date the patient attends Screening Visit 2.

Section C - BLOOD PRESSURE READINGS

Refer to the *Blood Pressure Management Protocol* section in Chapter 6, page 1 for any questions regarding blood pressure.

C.1 Supine Blood Pressure (after patient is lying for 5 minutes)

C.1.a Blood Pressure

If <90/70 mmHg, the patient is excluded from the study. See Form B01 (Eligibility and Exclusion Inventory), question D.8.

C.1.b Heart Rate

C.2 Standing Blood Pressure (immediately upon standing)

C.2.a Blood Pressure Reading 1

C.2.b Heart Rate 1

After waiting 2 minutes

C.2.c Blood Pressure Reading 2

C.2.d Heart Rate 2

Section D - ORTHOSTATIC HYPOTENSION

Refer to the *Orthostatic Hypotension* section in Chapter 6, page 2 for any questions.

D.1 Orthostatic Hypotension

If either standing systolic (question C.2.a or C.2.c) is 20 mmHg less than the supine systolic (question C.1.a)

OR if either standing diastolic (question C.2.a or C.2.c) is 10 mmHg less than the supine diastolic (question C.1.a)

OR if the patient has developed significant postural hypotension, record YES.

If this question is answered YES, the patient is ineligible for the study. See Form B01 (Eligibility and Exclusion Inventory), question D.13.

Section E - UROFLOW MEASUREMENTS

Have patient come for his visit with a full bladder. Instruct him to urinate into the white funnel. The machine will automatically begin recording at the initiation of flow and terminate at the end of micturition. (**Note:** this test should be performed when the patient has a normal desire to void and in conditions suitable for privacy.) Essentially, all the patient must do is urinate into the flowmeter while standing. Tell the patient no discomfort is associated with this test and the duration is several seconds. The Maximum Flow Rate must be equal to two seconds (i.e., 2 dots along the bottom of the uroflow strip). **Voided volume must be at least 125 ml for the test to be valid**

The information required for the case report form follows the uroflow strip in the order of information on the printout (items #1-6). Only the post void residual (item #7) must be obtained from the bladder scan printout. Transcribe the uroflow results onto the case report form, making sure that units of measurement are the same. Be certain to right-justify all numbers. The same applies to the post void residual - check units of measurement, right-justify, etc.

If the bladder scan machine in use provides a printout, this must also be maintained. If there is no printout from the bladder scan, a notation of the PVR must be made in the source document.

Mark the date and patient number (screening or study number) on each uroflow printout. Make two copies of all printouts. One copy is to be maintained in the source document. The other copy along with the original printout is placed in the envelope in the patient's binder.

See the *Uroflowmetry Procedure* section in Chapter 7, page 1 for any questions regarding this procedure.

E.1 Voiding Time

E.2 Flow Time

E.3 Time to Maximum Flow

E.4 Maximum Flow Rate

If this value is <4.0 or >15.0 ml/sec, the patient is ineligible for the study. See Form B01 (Eligibility and Exclusion Inventory), question C.3.

E.5 Mean Flow Rate

E.6 Voided Volume

If this value is <125 ml, the patient is ineligible for the study. See Form B01 (Eligibility and Exclusion Inventory), question C.3.

E.7 Post Void Residual

INSTRUCTIONS FOR COMPLETING FORM B04 - RANDOMIZATION INFORMATION

This form should be completed if the patient has attended Screening Visits 1 and 2, all laboratory results are returned, the patient is still eligible for the study, and the patient attends a randomization visit.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of Randomization Visit

Record the date of the visit at which the patient will be randomized (the date of the visit).

B.2 Date of Screening Visit 1

Record the date of Screening Visit 1. See Form B02 (Screening Visit 1 Inventory), question B.1 and Form B01 (Eligibility and Exclusion Inventory), question B.1.

Section C - ELIGIBILITY ASSESSMENT

For questions C.1-C.3.c, if the question is answered NO, the patient cannot be randomized until the issue is resolved. If the issue cannot be resolved, the patient will not be randomized.

C.1 Is the patient eligible?

Record YES if the questions E.1 and E.2 on Form B01 (Eligibility and Exclusion Inventory) are answered YES.

C.2 Has the patient signed the informed consent form?

Record YES if the patient has signed the informed consent. See Form B01 (Eligibility and Exclusion Inventory), question C.1.

C.3 Have the following forms been completed:

The following forms must be completed and entered into the microcomputer in order to perform computerized randomization.

C.3.a Eligibility/Exclusion Inventory

Record YES if Form B01 is completed.

C.3.b Screening Visit 1 Inventory

Record YES if Form B02 is completed.

C.3.c Screening Visit 2 Inventory

Record YES if Form B03 is completed.

For Questions C.4 and C.5, if the question is answered NO, the patient cannot be randomized. These issues are not resolvable. If the patient is a good candidate, but exceeded the 6 week pre-randomization period, it is possible to randomize the patient by repeating the screening period.

C.4 Has the patient successfully completed the placebo run-in phase?

Record YES if the patient has completed the placebo run-in phase in the opinion of the Coordinator. Refer to Form B05 (Medication Run-in Information).

C.5 Is the elapsed time from the date of the first pre-randomization visit to the randomization visit less than or equal to 6 weeks (42 days)?

Refer to questions B.1 and B.2, record YES if the time elapsed is less than or equal to 6 weeks (42 days).

Section D - BASELINE PROCEDURE

D.1 Were the results received from the Diagnostic Center for PSA and Hormones? Record YES if the results have been received from the Diagnostic Center.

If this question is answered NO, the patient's randomization is "on hold" until the issue is resolved. When the PSA results are received from the Diagnostic Center, the response to the question can be changed and the patient can proceed with randomization.

If question D.1 is answered YES, completed question D.1.a.

D.1.a PSA Value

Record the value of PSA reported by the Diagnostic Center.

If this value >10 ng/ml the patient is excluded from the study. See Form B01 (Eligibility and Exclusion Inventory), question D.10.

Section E - BLOOD PRESSURE READINGS

Refer to the *Blood Pressure Management Protocol* section in Chapter 6, page 1 for any questions regarding blood pressure.

E.1 Supine Blood pressure (after patient is lying for 5 minutes)

E.1.a Blood Pressure

If <90/70 mmHg, the patient is excluded from the study. See Form B01 (Eligibility and Exclusion Inventory), question D.8.

E.1.b Heart Rate

E.2 Standing Blood Pressure (immediately upon standing)

E.2.a Blood Pressure Reading 1

E.2.b Heart Rate 1

After waiting 2 minutes

E.2.c Blood Pressure Reading 2

E.2.d Heart Rate 2

Section F - ORTHOSTATIC HYPOTENSION

Refer to the *Orthostatic Hypotension* section in Chapter 6, page 2 for any questions.

F.1 Did the Patient Have Orthostatic Hypotension

If either standing systolic (question E.2.a or E.2.c) is 20 mmHg less than the supine systolic (question E.1.a) **OR** if either standing diastolic (question E.2.a or E.2.c) is 10 mmHg less than the supine diastolic (question

E.1.a)

OR if the patient has developed significant postural hypotension, record YES.

If this question is answered YES, the patient is ineligible for the study. See Form B01 (Eligibility and Exclusion Inventory), question D.13.

Section G - Perform computerized randomization

When this form is completed to this point, it must be keyed into the microcomputer in order to randomize the patient. When all information to this point is keyed, the computer will prompt for an 'X' at question G. If all documents (Forms B01, B02, B03, B05, Q01, Q03, and P01) are entered and the patient is eligible, the computer will randomize the patient and complete question G.1 with the Patient Study Number.

For some reason, if the patient is ineligible for the study as per the case report forms entered into the computer, the patient will not be randomized. In such a case, the computer will return a message to indicate the reason the patient cannot be randomized.

To avoid this the clinic staff can perform a mock randomization at anytime before attempting to randomize the patient (See Chapter 12, page 14). If a problem is found it can be researched and resolved before the actual randomization is attempted.

In such a case, if the problem can be rectified by keying a form into the computer for example, then the computer operator may escape this Form B04 and enter the missing form. If all problems are checked and rectified where possible, the keyer should randomize again.

G.1 BPH Study Number

If patient is randomized, record the study number allocated by the computer.

G.2 Number of doxazosin tablets dispensed today

If patient is randomized, record the number of doxazosin tablets dispensed at this first visit on coded medication. There should be 3 titration bottles (A, B, C), 10 tablets each, dispensed at this time.

Affix the doxazosin label to Form R03 in the space provided.

G.3 Number of finasteride tablets dispensed today

If patient is randomized, record the number of finasteride tablets dispensed at this first visit on coded medication. There should be 1 bottle of tablets dispensed at this time.

Affix the finasteride label to Form R03 in the space provided.

Refer to the *Dispensing* section of the *Medical Therapy Protocol* in Chapter 5, page 3 for any questions regarding doxazosin or finasteride dispensing or compliance.

INSTRUCTIONS FOR COMPLETING FORM B05 - MEDICATION RUN-IN INFORMATION

This form is to be started at Screening Visit 2 (initiation of run-in) and completed at the randomization visit (completion of run-in).

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - RUN-IN INITIATION INFORMATION

B.1 Date run-in initiated

Record the date the placebo run-in medications were dispensed to the patient. This should be at Screening Visit 2.

Affix labels from run-in to Form R03 when the medication is dispensed.

Section C - COMPLIANCE INFORMATION

C.1 Date run-in completed (date of randomization visit)

Record the date the run-in medication was returned. The run-in should be completed at the Randomization Visit.

C.2 Number of days since last visit

Count the days since the run-in medication was dispensed (question B.1) until the medication was returned (question C.1), the number of nights the patient should have taken the medication. If this number is less than 7 days, the patient is ineligible to be randomized at this point.

Section D - DOXAZOSIN COMPLIANCE

Refer to the *Dispensing* section of the *Medical Therapy Protocol* section in Chapter 5, page 3 for any questions regarding doxazosin dispensing or compliance.

D.1 Number of doxazosin run-in tablets dispensed

Record the number of doxazosin run-in tablets dispensed. Refer to the patient's dispensing record.

Affix the doxazosin label to Form R03 in the space provided.

D.2 Number of doxazosin run-in tablets returned

Record the number of run-in tablets the patient returned today. Refer to the patient's dispensing record. If the patient does not return any tablets, regardless of the reason, the number of tablets returned is zero.

D.3 Compliance

Calculate compliance by the formula:

$$\frac{\text{tablets dispensed (D.1)} - \text{tablets returned (D.2)}}{\text{days since last dispensing visit (question C)}} \times 100$$

Record this value. Be sure to round to the nearest whole percentage.

There are 4 spaces to record compliance. This allows for compliance up to 9999% OR a negative compliance (3 digits with the negative sign). Therefore, unless any of the numbers used to calculate compliance are blank, compliance must be entered. PLEASE NOTE THAT THIS IS DIFFERENT FROM THE PILOT STUDY.

Section E - FINASTERIDE COMPLIANCE

Refer to the *Dispensing* section of the *Medical Therapy Protocol* section in Chapter 5, page 3 for any questions regarding finasteride dispensing or compliance.

E.1 Number of finasteride run-in tablets dispensed

Record the number of finasteride run-in tablets dispensed. Refer to the patient's dispensing record.

Affix the finasteride label to Form R03 in the space provided.

E.2 Number of finasteride run-in tablets returned

Record the number of run-in tablets the patient returned today. Refer to the patient's dispensing record. If the patient does not return any tablets, regardless of the reason, the number of tablets returned is zero.

E.3 Compliance

Calculate compliance by the formula:

$$\frac{\text{tablets dispensed (E.1)} - \text{tablets returned (E.2)}}{\text{days since last dispensing visit (question C)}} \times 100$$

Record this value. Be sure to round to the nearest whole percentage.

There are 4 spaces to record compliance. This allows for compliance up to 9999% OR a negative compliance (3 digits with the negative sign). Therefore, unless any of the numbers used to calculate compliance are blank, compliance must be entered. PLEASE NOTE THAT THIS IS DIFFERENT FROM THE PILOT STUDY.

INSTRUCTIONS FOR COMPLETING FORM E01 - AUA SYMPTOM SCORE EVENT REPORT

This form should be started if the patient's AUA Symptom Score reaches the 4 point event flag on the patient label. Refer to the *Clinical Events Protocol* section in Chapter 6, page 6 for any questions regarding the clinical event recorded on this form.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - INITIAL VISIT INFORMATION

B.1 Date of Initial clinical event visit

Record the date of the visit at which the increased Symptom Score event was triggered.

B.2 Week of initial clinical event visit

Refer to the patient's study calendar and record the week number that corresponds to the date in question B.1.

B.3 Type of visit

Record an 'X' in the corresponding box for the type of visit.

Section II.A - Initial 4 point event visit

II.A.1 AUA symptom score

Record the AUA Symptom Score that triggered the 4 point event. See Form Q01 (AUA Symptom Score Questionnaire), page 2.

II.A.2 Is the value in A.1 greater than or equal to 4 points more than the baseline symptom score (see patient label)?

Refer to the patient label. Record YES if the value in question II.A.1 is greater than or equal to the AUA 4 point event flag. Record NO if it is less than the 4 point event flag.

If question II.A.2 is answered YES, continue.

II.A.3 Are corrective measures necessary?

Record YES if the patient was taking sinus medication, a new diuretic, has an infection, or there is another reason why the symptom score would have risen besides BPH.

If question II.A.3 is answered YES, corrective measures must be taken before continuing. After corrective measures have been taken, the patient should be scheduled for a confirming visit in no less than 2 weeks and no more than 4 weeks from the date in question I.B.1. Also complete question II.A.3a.

II.A.3.a What is the reason for corrective measures ?

Record an 'X' in the appropriate box for the reason for corrective measures. If corrective measures are required for some reason other than those listed, record an 'X' in the "other" box and specify the reason.

If there is no need for corrective measures, schedule the patient for a confirming visit in no less than 2 weeks and no more than 4 weeks from the date in question I.B.1.

Section II.B - Confirming 4 point event visit

This visit should be at least 2 weeks and not more than 4 weeks from the initial 4 point event visit in section II.A. At this visit, if it is not a scheduled quarterly visit, Form F03 (Interim Visit Checklist) should also be completed.

II.B.1 Date of Visit

Record the date of the confirming visit.

II.B.2 Week of Visit

Refer to the patient's study calendar and record the week of the confirming visit.

II.B.3 AUA symptom score

Record the AUA Symptom Score obtained at the confirming visit. See Form Q01 (AUA Symptom Score Questionnaire), page 2.

II.B.4 Is the value in B.3 greater than or equal to 4 points more than the baseline symptom score (see label)?

Refer to the patient label. Record YES if the value in question II.B.3 is greater than or equal to the AUA 4 point event flag. Record NO if it is less than the 4 point event flag.

If question II.B.4 is answered YES, this documents an AUA Symptom Score 4 Point Event. If the patient is taking coded medication, then coded medications may be discontinued at the discretion of the Principal Investigator.

II.B.5 AUA symptom score 4 point event declared?

Record YES if question II.B.4 is answered YES. Record NO if question II.B.4 is answered NO.

If question II.B.5 is answered YES, continue.

II.B.6 Is the patient on coded medications?

Record YES if the patient has been taking coded medication to date.

If question II.B.6 is answered YES, continue.

II.B.7 Will the coded medications be discontinued?

If the Principal Investigator decides that the coded medications will be discontinued, record YES. If they will not be discontinued, record NO.

If question II.B.7 is answered YES, continue.

II.B.8 Date coded medication discontinued

Record the date the coded medications were discontinued.

INSTRUCTIONS FOR COMPLETING FORM E02 - CREATININE RISE EVENT REPORT

This form should be completed if a patient has a 50% increase from baseline (1.5 times the baseline value) in serum creatinine that is at least 1.5 mg/dl. The flag for each patient is printed on the patient label. Refer to the *Clinical Events Protocol* section in Chapter 6, page 6 for any questions regarding the clinical events recorded on this form.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - INITIAL CREATININE RISE EVENT VISIT

B.1 Date of initial event visit

Record the date of the visit at which the rise in serum creatinine was obtained.

B.2 Week of initial event visit

Refer to the patient's study calendar and record the week number that corresponds to the date in question B.1.

B.3 Type of visit

Record an 'X' in the corresponding box for the type of visit.

B.4 Serum Creatinine

Record the serum creatinine result from question F.7 on Form F02 (Major Follow-up Visit Inventory).

B.5 Is the value in question B.4 greater than or equal to 1.5 times the baseline serum creatinine (see patient label) and greater than or equal to 1.5 mg/dl?

Refer to the patient label. Record YES if the value in question B.4 is greater than or equal to the creatinine rise flag and it is greater than or equal to 1.5 mg/dl.

If question B.5 is answered YES, schedule the patient for a confirming visit within 4 weeks and continue.

Section C - CONFIRMING CREATININE RISE EVENT VISIT

Also complete Form F03 (Interim Visit Checklist) at this visit.

C.1 Date of Visit

Record the date of the confirming visit. This date should be the same as the date on the corresponding Form F03 (Interim Visit Checklist), question B.1.

C.2 Week of Visit

Refer to the patient's study calendar and record the week number that corresponds to the date in question C.1.

C.3 Serum Creatinine

Record the serum creatinine result from the confirming visit.

C.4 Is the value in question C.3 greater than or equal to 1.5 times the baseline serum creatinine (see patient label) and greater than or equal to 1.5 mg/dl?

Refer to the patient label. Record YES if the value in C.3 is greater than or equal to the creatinine rise flag and it is greater than or equal to 1.5 mg/dl.

If question C.4 is answered YES, this documents a creatinine rise event.

C.5 Creatinine rise event declared?

Record YES if question C.4 is answered YES.

If question C.5 is answered YES, continue.

C.6 Is the patient on coded medications?

Record YES if the patient is taking coded medications.

If question C.6 is answered YES, STOP ALL CODED MEDICATIONS and continue.

C.7 Date coded medication discontinued

Record the date the coded medications were discontinued.

INSTRUCTIONS FOR COMPLETING FORM E03 - URINARY EVENT REPORT

This form should be completed if the patient experiences an acute urinary retention event, a recurrent urinary tract infection / urosepsis event or an incontinence event. Refer to the *Clinical Events Protocol* section in Chapter 6, page 6 for any questions regarding the clinical events recorded on this form.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - INITIAL VISIT INFORMATION

B.1 Date of initial event visit

Record the date of the initial visit for the urinary event.

B.2 Week of initial event visit

Refer to the patient's study calendar and record the week number that corresponds to the date in question B.1.

B.3 Type of visit

Record an 'X' in the corresponding box for the type of visit.

Section C - URINARY EVENT IDENTIFICATION

C.1 Type of event

Record an 'X' in the box that corresponds to the appropriate event (Acute Urinary Retention, Recurrent Urinary Tract Infection / Urosepsis or Incontinence).

Part II - ACUTE URINARY RETENTION EVENT

Complete this part if question I.C.1 is answered "1": if the patient is unable to urinate and requires a catheter.

II.A.1 Date of catheterization

Record the date the patient was catheterized.

II.A.2 Is there an obvious cause of urinary retention other than BPH (e.g., alpha sympathomimetic medications or anesthesia)?

Record YES if there is an obvious cause of retention other than BPH.

If question II.A.2 is answered YES, remove catheter and patient should try to void. Complete question II.A.2a.

If question II.A.2 is answered NO, SKIP to question 3.

II.A.2.a Is the patient able to void with the catheter removed?

Record YES if the catheter was removed and the patient was able to void. Record NO, if the patient still could not void.

If question II.A.2a is answered YES, this event should be recorded as an adverse event (complete Form E05 Adverse Event Report, and E06, Serious Adverse Event Report if necessary) but DO NOT STOP CODED MEDICATION.

If question II.A.2 is answered NO, or II.A.2a is answered NO, the Clinical Review Committee must be consulted to declare an Acute Urinary Retention Event.

II.A.3 Acute urinary retention event declared?

Record YES, if the CRC confirmed an Acute Urinary Retention Event.

If question II.A.3 is answered YES, continue.

II.A.4 Date of confirmation by Clinical Review Committee

Record the date of confirmation by the CRC.

II.A.5 Is the patient on coded medications?

Record YES if the patient is taking coded medications.

If question II.A.5 is answered YES, STOP ALL CODED MEDICATIONS and continue.

II.A.6 Date coded medication discontinued

Record the date the coded medications were discontinued. This is not necessarily the date confirmed and should not be before the confirmation date.

Part III - RECURRENT URINARY TRACT INFECTION / UROSEPSIS EVENT

Complete this part if question I.C.1 is answered "2"; if the patient has had 2 positive urinalysis cultures within 1 year or a single episode of urosepsis.

III.A.1 Has the patient had two positive cultures within 1 year?

Record YES if the patient has had two documented positive cultures within one year.

If question III.A.1 is answered YES, continue. If NO, skip to question 2.

III.A.1.a Date of first positive culture

Record the date of the first positive culture.

III.A.1.b Date of negative culture

The two positive cultures must be separated by a documented negative culture. Record the date of the negative culture.

III.A.1.c Date of second positive culture

Record the date of the second positive culture. This should be within 1 year of the first positive culture.

III.A.2 Has the patient had a single episode of urosepsis due to bladder outlet obstruction documented by a positive culture?

Record YES if the patient has had a positive culture for a single episode of urosepsis due to bladder outlet obstruction.

If question III.A.2 is answered YES, continue. If NO, skip to question 3.

III.A.2.a Date of positive culture

Record the date of the positive culture.

Consultation with the CRC is necessary to declare a recurrent urinary tract infection / urosepsis event.

III.A.3 Recurrent urinary tract infection / Urosepsis event declared?

Record YES if the CRC confirmed a Recurrent Urinary Tract Infection / Urosepsis Event.

If question III.A.3 is answered YES, continue.

III.A.4 Date of confirmation by Clinical Review Committee

Record the date the CRC confirmed the event.

This documents a Recurrent Urinary Tract Infection / Urosepsis Event.

III.A.5 Is the patient on coded medications?

Record YES if the patient is taking coded medication.

If question III.A.5 is answered YES, STOP ALL CODED MEDICATIONS and continue.

III.A.6 Date coded medication discontinued

Record the date the coded medications were discontinued. This is not necessarily the date confirmed and should not be before the confirmation date.

Part IV - INCONTINENCE EVENT

Complete this part if question I.C.1 is answered "3"; if the patient has had an involuntary loss of urine that is socially or hygienically unacceptable.

IV.A.1 Has the patient had an involuntary loss of urine that is socially or hygienically unacceptable?

Record YES if the patient has had an involuntary loss of urine that is socially or hygienically unacceptable as determined by the patient and/or physician.

If question IV.A.1 is answered YES, continue. Consultation with the CRC is necessary to declare an Incontinence Event.

IV.A.2 Incontinence event declared?

Record YES if the CRC declared an Incontinence Event.

If question IV.A.2 is answered YES, continue.

IV.A.3 Date of confirmation by the Clinical Review Committee

Record the date the CRC confirmed the event.

This documents an Incontinence Event.

IV.A.4 Is the patient on coded medications?

Record YES if the patient is taking coded medications and stop all coded medications.

If question IV.A.4 is answered YES, continue.

IV.A.5 Date coded medication discontinued

Record the date the coded medications were discontinued.

INSTRUCTIONS FOR COMPLETING FORM E04 - ADVERSE EVENT REPORT

Complete this form if the patient has had any adverse experiences, drug reactions, side effects, abnormal laboratory values, hospitalizations, other complications or pre-existing conditions that worsened. (If this is a Standard or Major Follow-up Visit, question I.1 on Form F01 should be answered YES or if it is a Titration Visit, question I.1 on Form F06 should be answered YES). Refer to the *Adverse Event Reporting* section in Chapter 6, page 14 for any questions regarding the recording and reporting of adverse events.

If this is a serious event, this form should be FAXED to the Biostatistical Coordinating Center IMMEDIATELY.

Section A - REPORT IDENTIFICATION

A.1 - A.4 See *Instructions for completing Patient Identification* on page 1 of this chapter.

A.5 Date of report

Record the date the report is being completed.

A.6 Date of onset of adverse experience

Record the date of the onset of the adverse experience. If this is a follow-up report to a previously documented adverse experience, the date of onset should be the same as the date of the onset on the initial report.

A.7 Type of report

Record an 'X' in the appropriate box. If this is the first report on the particular event, it is an initial report. If it is any subsequent report for the same adverse event, the type of report is a follow-up.

If information was temporarily missing on an initial report, that report should be updated with the new information instead of completing a follow-up report.

Section B - GENERAL CLASSIFICATION

B.1.a. Adverse experience (short description)

Record a simple, very short description of the event. This should not include dates or circumstances, only the

event.

B.1.b. COSTART description (See COSTART Term Coding Glossary)

Consult the COSTART Term Coding Glossary to choose the glossary term that best describes the Adverse Event short description in Question B.1.a.

B.2 Did the adverse experience result in:

Record an 'X' in all appropriate boxes.

If event was a death, continue. If not, SKIP to question 3.

B.2.a Date of death

Record the date of death.

B.2.b Probable cause of death

Record the probable cause of death.

B.3 Was the adverse experience:

Record an 'X' in all appropriate boxes.

IF ANY ITEM IN B.2 OR B.3 IS CHECKED, CONTACT THE BIostatistical COORDINATING CENTER STAFF IMMEDIATELY AT (301) 881-9260 AND FAX THE FORM.

Section C - EVENT INFORMATION

C.1 Onset of adverse experience

Record an 'X' in the appropriate box that corresponds to the type of the onset of the adverse experience.

C.2 Was the patient on coded medication at the time of the adverse experience?

Record YES if the patient was taking coded medication at the time of the adverse experience. If medications were discontinued due to the adverse experience, the patient was on coded medication at the time of the adverse experience.

Note: Placebo run-in medications are not coded medications.

If question C.2 is answered YES, continue.

If question C.2 is answered NO, SKIP to question 3.

C.2.a Was the adverse experience related to coded medication?

Record an 'X' in the box corresponding to the physician's best estimate of the relationship to coded medication.

C.2.b Were the coded medication interrupted or stopped?

Record YES if the coded medications were stopped or interrupted for any period of time. If question is answered NO, skip to question 3.

If question C.2 is answered YES, continue.

C.2.b.i Which coded medication(s) was interrupted or stopped? (Check all that apply)

Record an 'X' in the doxazosin box if doxazosin coded medication was discontinued. Record an 'X' in the finasteride box if finasteride coded medication was discontinued.

C.2.b.ii Was the adverse experience reversible when the coded medications were withdrawn?

Record YES if the experience was reversible when coded medications were discontinued (i.e. if the symptoms disappeared).

C.2.b.iii Were the coded medications re-started?

Record YES if the coded medications were re-started.

If question C.2.b.ii is answered YES, continue. If question C.2.b.iii is answered NO, SKIP to question 3.

C.2.b.iii.a Which coded medication(s) was re-started? (Check all that apply)

Record an 'X' in the doxazosin box if doxazosin coded medication was discontinued. Record an 'X' in the finasteride box if finasteride coded medication was discontinued.

C.2.b.iii.b How long was the patient off coded medications?

Record how long the patient was off coded medications as a number and units (i.e. days, weeks or months).

If the patient was off coded doxazosin for more than 3 days, it must be re-titrated when re-challenging.

C.2.b.iii.c Did the symptoms recur?

Record YES if the symptoms recurred after re-challenging.

C.3 Was the patient taking any medication other than the coded medications within 14 days of the onset of the adverse experience?

Record YES if the patient was taken any medication at all other than coded medications within 14 days before the event.

If question C.3 is answered YES, continue.

C.3.a - j List below:

Record all medications, doses and start and stop dates with as much information as is available.

C.4 Describe the adverse experience in detail:

Record a more detailed description than Question B.1 including dates and all pertinent information.

Check only one box for questions C.5 through C.8.

C.5 Overall severity of adverse experience

Record an 'X' in the most appropriate box.

C.6 Duration of adverse experience

Record an 'X' in the most appropriate box.

C.7 Treatment administered for the adverse experience

Record an 'X' in the most appropriate box.

C.8 Outcome:

Record an 'X' in the most appropriate box.

Section D - CONCLUSION

D.1 Additional comments:

If there are any additional comments, record them here.

INSTRUCTIONS FOR COMPLETING FORM E05 - ADVERSE EVENT REPORT

This form is to be completed if the patient has had any adverse experiences, drug reactions, side effects, abnormal laboratory values, hospitalizations, other complications or worsening of pre-existing conditions. If an adverse event is serious, the Serious Adverse Event Report (Form E06) must also be completed.

If this is a Standard or Major Follow-up Visit, question I.1 on Form F01 should be answered YES or if it is a Titration Visit, question I.1 on Form F06 should be answered YES. Refer to the *Adverse Event Reporting* section in Chapter 6, page 14 for any questions regarding the recording and reporting of adverse events.

If the event is serious, the pages associated with the serious event should be faxed to the BCC with the Serious Adverse Event Report (Form E06).

Section A - PATIENT IDENTIFICATION

A.1 - A.4 See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of report

Record the date the report is being completed. This should be the same date the adverse event was reported to the clinic.

B.2 Type of visit

Record an 'X' in the appropriate box.

B.3 If follow-up, week of visit

Refer to the patient's study calendar and record the week number that corresponds to the date in question B.1.

Section C - ADVERSE EVENT SUMMARY - Events 1-12

For each event, the following information is collected.

Adverse Event (short description)

Record a simple, very short description of the event. This should not include dates or circumstances, only the event.

COSTART Term (See COSTART Term Coding Glossary)

Consult the COSTART Term Coding Glossary to choose the glossary term that best describes the Adverse Event short description.

Onset Date

Record the date of the onset of the adverse event.

Date Resolved / Continuing

If the event resolved, record the date of resolution. If the event has not resolved as of the report date, record an 'X' in the "continuing" box.

Note: If the adverse event is continuing and becomes resolved at a future date, another Form E05 needs to be completed.

Was the event serious?

Record '1' for YES if the event was serious. Serious adverse events are congenital anomaly, cancer, life-threatening, due to an overdose, or result in death, required or prolonged hospitalization, permanent disability, or treatment to prevent a serious adverse event. For each serious adverse event, also complete the Serious Adverse Event Report (Form E06).

On coded medication?

Record '1' for YES if the patient was taking coded medication at the time of the adverse experience. If medications were discontinued due to the adverse experience, the patient was on coded medication at the time of the adverse experience.

Note: Placebo run-in medications are not considered coded medications.

If answered YES, continue.

If answered NO, SKIP to the next event.

Relationship to coded medication

Record the appropriate number (1,2,3,4) that corresponds to the physician's best estimate of the relationship to coded medication.

Interrupted or stopped?

Record '1' for YES if the coded medications were stopped or interrupted for any period of time as a result of this adverse experience. Record '2' for NO if the coded medications were not interrupted in anyway and skip to the next event.

If YES, which medication?

Record the number (1,2,3) in the box corresponding to the coded medication(s) which were discontinued in association with the specific adverse event.

INSTRUCTIONS FOR COMPLETING FORM E06 - SERIOUS ADVERSE EVENT REPORT

Complete this form for any event on the Adverse Event Report (Form E05) that is serious.

Notify the Biostatistical Coordinating Center IMMEDIATELY and fax this form to (301) 881-3589.

Section A - REPORT IDENTIFICATION

A.1 - A.4 See *Instructions for completing Patient Identification* on page 1 of this chapter.

A.5 Date of report

Record the date the report is completed. This should be the same date the adverse event was reported to the clinic. This date must be the same as the report date recorded on Form E05.

A.6 Date of onset of adverse experience

Record the date of the onset of the adverse experience. (If this is a follow-up report to a previously documented adverse experience, the date of onset should be the same as the date of the onset on the initial report). This date must be the same as the onset date recorded on Form E05.

A.7 Type of report

Record an 'X' in the appropriate box. If this is the first report on the particular event, it is an initial report. If it is any subsequent report for the same adverse event, the type of report is a follow-up. If information was temporarily missing on an initial report, that report should be updated with the new information instead of completing a follow-up report.

A.8 Event Number (See Form E05)

Record the number of the event corresponding to the event number listed on the Adverse Event Report (Form E05).

Section B - GENERAL CLASSIFICATION

B.1.a. Adverse experience (short description)

Record a simple, very short description of the event. This should not include dates or circumstances, only the event. This description must be the same as the short description listed on Form E05.

B.1.b. COSTART description (See COSTART Term Coding Glossary)

Consult the COSTART Term Coding Glossary to choose the glossary term that best describes the Adverse Event short description in Question B.1.a. The COSTART description must be the same as the COSTART description listed on Form E05.

B.2 Did the adverse experience result in:

Record an 'X' in all appropriate boxes indicating death, required or prolonged hospitalization, and/or permanent or severe disability.

If event was a death, continue. If not, SKIP to question B.3.

B.2.a Date of death

Record the date of death.

B.2.b Probable cause of death

Record the probable cause of death.

B.3 Was the adverse experience:

Record an 'X' in all appropriate boxes indicating congenital anomaly, cancer, life-threatening, due to an overdose, and/or treatment to prevent a serious event.

AT LEAST ONE ITEM IN QUESTIONS B.2 OR B.3 MUST BE CHECKED.

CONTACT THE BIOSTATISTICAL COORDINATING CENTER STAFF IMMEDIATELY AT (301) 881-9260 AND

FAX THE FORM TO (301) 881-3589.

Section C - EVENT INFORMATION

C.1 Onset of adverse experience

Record an 'X' in the appropriate box that corresponds to the type of the onset of the adverse experience.

C.2 Was the coded medication interrupted or stopped?

Record YES if the coded medications were stopped or interrupted for any period of time as a result of this adverse experience. This question should be answered the same as the similar question on Form E05.

If question C.2 is answered NO, skip to question C.3.

If question C.2 is answered YES, continue.

C.2.a Was the adverse experience reversible when the coded medication(s) was withdrawn?

Record YES if the experience was reversible when coded medications were discontinued (i.e. if the symptoms disappeared).

C.2.b Were the coded medications re-started?

Record YES if the coded medications were re-started.

If question C.2.b is answered NO, SKIP to question C.3.

If question C.2.b is answered YES, continue.

C.2.b.i Which coded medication(s) was re-started? (Check all that apply)

Record an 'X' in the doxazosin box if doxazosin coded medication was restarted. Record an 'X' in the finasteride box if finasteride coded medication was restarted.

C.2.b.ii How long was the patient off coded medications?

Record how long the patient was off coded medications as a number and units (i.e. days, weeks or months).

If the patient was off coded doxazosin for more than 3 days, it must be re-titrated when re-challenging (Refer to Dispensing section in Chapter 5, page 3 for retitration).

C.2.b.iii Did the symptoms recur?

Record YES if the symptoms recurred after re-challenging.

C.3 Was the patient taking any medication other than the coded medications within 14 days of the onset of the adverse experience?

Record YES if the patient was taken any medication other than coded medications within 14 days before the event.

If question C.3 is answered YES, continue.

C.3.a - j List below

Record all medications, doses and start and stop dates with as much information as is available.

C.4 Describe the adverse experience in detail:

Record a more detailed description than Question B.1 including dates and all pertinent information.

Check only one box for questions C.5 through C.8.

C.5 Overall severity of adverse experience

Record an 'X' in the most appropriate box.

C.6 Duration of adverse experience

Record an 'X' in the most appropriate box.

C.7 Treatment administered for the adverse experience

Record an 'X' in the most appropriate box.

C.8 Outcome:

Record an 'X' in the most appropriate box.

Section D - CONCLUSION

D.1 Additional comments:

If there are any additional comments, record them here.

INSTRUCTIONS FOR COMPLETING FORM F01 - STANDARD FOLLOW-UP VISIT INVENTORY

This form should be completed at all quarterly follow-up visits. This does not include any titration visits.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of Visit

Record the date the patient attends the follow-up visit.

B.2 Week of Visit

Refer to the patient's study calendar and record the week number that corresponds to the date in Question B.1.

Section C - BLOOD PRESSURE READINGS

Refer to the *Blood Pressure Management Protocol* section in Chapter 6, page 1 for any questions regarding blood pressure.

C.1 Supine Blood Pressure (after patient is lying for 5 minutes)

C.1.a Blood Pressure

C.1.b Heart Rate

C.2 Standing Blood Pressure (immediately upon standing)

C.2.a Blood Pressure 1

C.2.b Heart Rate 1

After waiting 2 minutes

C.2.c Blood Pressure 2

C.2.d Heart Rate 2

Section D - ORTHOSTATIC HYPOTENSION

Refer to the *Orthostatic Hypotension* section in Chapter 6, page 2 for any questions.

D.1 Orthostatic Hypotension

If either standing systolic (question C.2.a or C.2.c) is 20 mmHg less than the supine systolic (question C.1.a)

OR if either standing diastolic (question C.2.a or C.2.c) is 10 mmHg less than the supine diastolic (question C.1.a)

OR if the patient has developed significant postural hypotension, record YES.

Section E - Number of days since last visit

Refer to the patient's study calendar and count the days since the patient last attended a scheduled or interim follow-up visit.

Section F - DOXAZOSIN COMPLIANCE

Refer to the *Dispensing* section of the *Medical Therapy Protocol* section in Chapter 5, page 3 for any questions regarding doxazosin dispensing or compliance.

F.1 Dose of doxazosin

Record the appropriate dose of doxazosin currently being taken. If the patient is changing doses, record the dose the patient was taking until today's visit.

F.2 Number of doxazosin tablets dispensed at the last visit

Record the number of doxazosin tablets dispensed at the last visit (scheduled or interim). Refer to the patient's dispensing record.

F.3 Number of doxazosin tablets returned today

Record the number of tablets the patient returned today. Refer to the patient's dispensing record. If the patient does not return any tablets, regardless of the reason, the number of tablets returned is zero.

F.4 Compliance

Calculate compliance by the formula:

$$\frac{\text{tablets dispensed (F.2)} - \text{tablets returned (F.3)}}{\text{days since last dispensing visit (question E)}} \times 100$$

Record this value. Be sure to round to the nearest whole percentage.

There are 6 spaces to record compliance. This allows for compliance up to 999999% OR a negative compliance (5 digits with the negative sign). Therefore, unless any of the numbers used to calculate compliance are blank, compliance must be entered. PLEASE NOTE THAT THIS IS DIFFERENT FROM THE PILOT STUDY.

If you answer question F.4 is <80% compliance, counsel the patient.

F.5 Number of doxazosin tablets dispensed today

Record the number of tablets dispensed today. Refer to the patient's dispensing record.

Affix the label from the doxazosin tablets dispensed today to the appropriate page of Form R03.

Section G - FINASTERIDE COMPLIANCE

Refer to the *Dispensing* section of the *Medical Therapy Protocol* section in Chapter 5, page 3 for any questions regarding finasteride dispensing or compliance.

G.1 Number of finasteride tablets dispensed at the last visit

Record the number of finasteride tablets dispensed at the last visit (scheduled or interim). Refer to the patient's dispensing record.

G.2 Number of finasteride tablets returned today

Record the number of tablets the patient returned today. Refer to the patient's dispensing record. If the patient does not return any tablets, regardless of the reason, the number of tablets returned is zero.

G.3 Compliance

Calculate compliance by the formula:

$$\frac{\text{tablets dispensed (G.2)} - \text{tablets returned (G.3)}}{\text{days since last dispensing visit (question E)}} \times 100$$

Record this value. Be sure to round to the nearest whole percentage.

There are 6 spaces to record compliance. This allows for compliance up to 999999% OR a negative compliance (5 digits with the negative sign). Therefore, unless any of the numbers used to calculate compliance are blank, compliance must be entered. PLEASE NOTE THAT THIS IS DIFFERENT FROM THE PILOT STUDY.

If the answer to question G.4 is <80% compliance, counsel the patient.

G.4 Number of finasteride tablets dispensed today

Record the number of tablets dispensed today. Refer to the patient's dispensing record.

Affix the label from the finasteride tablets dispensed today to the appropriate page of Form R03.

Section H - CONCOMITANT MEDICATIONS

H.1 Is the patient taking coded doxazosin?

Record YES if the patient is currently taking coded doxazosin. A patient currently taking doxazosin took the medication within 24 hours prior to the visit.

H.2 Is the patient taking the coded finasteride?

Record YES if the patient is currently taking coded finasteride. A patient currently taking finasteride took the medication within 24 hours prior to the visit.

H.3 Is the patient taking any medication other than the coded medications?

Record YES if the patient is taking any medication other than the coded medications today. Remember this is a "snap-shot" of medications; just record the medications being taken today (NOT all medications taken since last visit).

If Question H.3 is answered YES, complete question H.3.a-j.

H.3.a-j List all medications, consulting PDR for spelling and *Exclusionary Medication* section (Chapter 6, page 3) for excluded medications.

Refer to the Concomitant Medication Dictionary for the proper recording of names and form of concomitant medications.

H.4 Has the patient taken viagra (sildenafil citrate) since the last visit?

Record YES if the patient has taken viagra since his last scheduled or interim visit.

Section I - ADVERSE EVENTS

Refer to the *Clinical Events Protocol* section in Chapter 6, page 6 for any questions regarding adverse events and how to report them.

I.1 Since the last scheduled follow-up visit, has the patient had any adverse experiences, drug reactions, side effects, abnormal laboratory values, hospitalizations, other complications or pre-existing conditions that worsened?

Please ask the patient about Adverse Events using the wording on the form, so as not to bias his answer.

Laboratory changes include those values considered to be out of normal range, that are clinically significant (as determined by a physician) or those not immediately explainable.

Adverse events are not intended to include the fluctuation of symptoms associated with bladder outlet obstruction (BPH). This information is captured on CRFs, but are not considered to be adverse events unless they seem unusual or unexplainable. If this question is answered YES, also complete Form E05 (Adverse Event Report) and if necessary, Form E06 (Serious Adverse Event Report).

Section J - UROFLOW MEASUREMENTS

Have patient come for his visit with a full bladder. Instruct him to urinate into the white funnel. The machine will automatically begin recording at the initiation of flow and terminate at the end of micturition. (**Note:** this test should be performed when the patient has a normal desire to void and in conditions suitable for privacy.) Essentially, all the patient must do is urinate into the flowmeter while standing. Tell the patient no discomfort is associated with this test and the duration is several seconds. The Maximum Flow Rate must be equal to two seconds (i.e., 2 dots along the bottom of the uroflow strip). **Voided volume must be at least 125 ml for the test to be valid**

The information required for the case report form follows the uroflow strip in the order of information on the printout (items #1-6). Only the post void residual (item #7) must be obtained from the bladder scan printout. Transcribe the uroflow results onto the case report form, making sure that units of measurement are the same. Be certain to right-justify all numbers. The same applies to the post void residual - check units of measurement, right-justify, etc.

If the bladder scan machine in use provides a printout, this must also be maintained. If there is no printout from the bladder scan, a notation of the PVR must be made in the source document.

Mark the date and patient number (screening or study number) on each uroflow printout. Make two copies of all printouts. One copy is to be maintained in the source document. The other copy along with the original printout is placed in the envelope in the patient's binder.

See the *Uroflowmetry Procedure* section in Chapter 7, page 1 for any questions regarding this procedure.

- J.1 Voiding Time**
- J.2 Flow Time**
- J.3 Time to Maximum Flow**
- J.4 Maximum Flow Rate**
- J.5 Mean Flow Rate**
- J.6 Voided Volume**
- J.7 Post Void Residual**

INSTRUCTIONS FOR COMPLETING FORM F02 - MAJOR FOLLOW-UP VISIT INVENTORY

This form should be completed annually or at the End of Study Visit. If a patient is in the biopsy substudy, all procedures and questionnaires must be completed before the biopsy is performed.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of Visit

Record the date the patient attends the Major Follow-up Visit.

B.2 Week of Visit

Refer to the patient's study calendar and record the week number that corresponds to the date in question B.1.

Section C - PHYSICAL EXAMINATION

The physician will document the examinations in the source document. A photocopy of page 5 from the case report form will help to serve as a guideline while the physician is conducting the exam.

C.1 Height

Record the patient's height in inches. It should be obtained without shoes.

C.2 Weight

Record the patient's weight in pounds (lbs). It should be obtained in lightweight clothing without shoes.

C.3 Examinations

The eight systems of the body will be reviewed by the physician, who will check either normal or abnormal. An abnormal check must be accompanied by a comment in the source document.

C.3.a Head, Ears, Nose, Throat

C.3.b Eyes

C.3.c Neck (include bruits)

C.3.d Heart

C.3.e Lungs and respiration

C.3.f Abdomen (include bruits)

C.3.g Liver

C.3.h Skin

C.3.i Neurological

C.3.j Urogenital

C.4 Rectal Examination

NOTE: SERUM FOR PSA MUST BE DRAWN BEFORE THE RECTAL EXAM.

C.4.a Prostate size

During the digital rectal exam, the physician must estimate the prostate size in grams.

For the rest of the rectal examination, record YES or NO. Any answer of YES will require further explanation in the source document.

- C.4.b Nodules or indurations**
- C.4.c Asymmetry**
- C.4.d Suspicious for cancer**
- C.4.e Tenderness**

Section D - PSA SERUM SPECIMEN

Refer to the *Serum Collection for PSA and Hormones* section in Chapter 7, page 3 for any questions regarding specimen collection.

D.1 Date sent to the Diagnostic Center

Record the date the serum specimen was sent to the Diagnostic Center. This may not necessarily be the same date it was collected.

Section E - COMPLETE BLOOD COUNT

Record the laboratory results, taking care to convert the value to the units on the case report form when necessary. Refer to *Serum Collection for Hematology and Chemistries* section in Chapter 7, page 4 for any questions regarding serum collection.

E.1 Leucocyte Count (WBC)

Record the value in $10^3/\text{ul}$.

E.2 Erythrocyte Count (RBC)

Record the value in $10^6/\text{ul}$.

E.3 Hemoglobin

Record the value in g/dl.

E.4 Hematocrit

Record the value as a percentage (%).

E.5 Platelet Count

Record the value in $10^3/\text{ul}$.

Section F - SERUM CHEMISTRIES

Record the laboratory results, taking care to convert the value to the units on the case report form when necessary. Refer to *Serum Collection for Hematology and Chemistries* section in Chapter 7, page 4 for any questions regarding serum collection.

F.1 Sodium

Record the value in mmol/L.

F.2 Potassium

Record the value in mmol/L.

F.3 Chloride

Record the value in mmol/L.

F.4 Bicarbonate

Record the value in mEq/L.

F.5 Glucose

Record the value in mg/dl.

F.6 Urea Nitrogen

Record the value in mg/dl.

F.7 Creatinine

Record the value in mg/dl.

If the creatinine is greater than or equal to 1.5 times the baseline creatinine and greater than or equal to 1.5 mg/dl, begin the Creatinine Rise Event Protocol and Form E02 (Creatinine Rise Event Report). Refer to the patient label for the flag value.

F.8 Uric Acid

Record the value in mg/dl.

F.9 Calcium

Record the value in mg/dl.

F.10 Phosphorus

Record the value in mg/dl.

F.11 ALT (SGPT)

Record the value in U/L.

F.12 Alkaline Phosphatase

Record the value in U/L.

F.13 Total Bilirubin

Record the value in mg/dl.

F.14 Total Protein

Record the value in g/dl.

F.15 Albumin

Record the value in g/dl.

F.16 Cholesterol

Record the value in mg/dl.

Section G - URINALYSIS

Refer to *Urinalysis Protocol* section in Chapter 7, page 4 for any questions regarding urinalysis.

G.1 Dipstick

Compare the reagent areas on the dipstick with the corresponding color chart on the bottle. Record the following dipstick readings.

G.1.a pH

G.1.b Glucose

G.1.c Blood

If this result is >0, be sure to complete Section F.2 (Microscopic Urinalysis).

G.1.d Ketones

G.1.e Protein

G.1.f Leucocyte Esterase

If this result is >0, be sure to complete Section F.2 (Microscopic Urinalysis).

G.2 If dipstick is positive (greater than 0) for blood or leucocyte esterase, please send specimen for microscopic urinalysis. Please use the following table to code the results.

1	None, Negative, WNL
2	1-5, Trace, Present, Slight, Rare, Occ
3	6-15, Moderate
4	16-30, Many, Frequent
5	> 30, Innumerable, TNTC

G.2.a WBC

G.2.b RBC

G.2.c Epithelial Cells

G.2.d Mucous

G.2.e Bacteria

G.2.f Casts - Hyaline

G.2.g Casts - Other

INSTRUCTIONS FOR COMPLETING FORM F03 - INTERIM VISIT CHECKLIST

This form should be completed at any visit that is not a scheduled follow-up visit. Additionally, this form should be completed if medications are mailed to the patient. This is the only situation for which the form is completed when the patient does not attend a clinic visit. (**Note:** It is acceptable to mail coded medications for one missed follow-up visit. It is unacceptable to do so for two or more consecutive missed visits.)

If the interim visit falls within the window for a standard or major follow-up visit, it is regarded as that follow-up visit. The appropriate procedures for that type of visit should be performed and the case report forms completed. In cases where an interim visit falls within a scheduled visit window, Form F03 should not be completed.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of Visit

Record the date the patient attends the interim visit.

B.2 Week of Visit

Refer to the patient's study calendar and record the week number that corresponds to the date in question B.1.

Section C - REASON FOR INTERIM VISIT

Please note that in many cases, there may be multiple reasons selected. For example, if a patient is having a PSA draw and there is an underlying reason for the draw (e.g., adverse event of elevated PSA), both the adverse event and blood draw boxes should be checked. Likewise, if the patient comes in for a biopsy because of an abnormal DRE, both the adverse event and TRUS and biopsy reasons should be selected.

C.1 AUA Symptom Score 4 Point Event

Record an 'X' in the corresponding box if the interim visit is scheduled to confirm a documented increase in the AUA symptom score of 4 or more points greater than the baseline symptom score (see patient label). Also complete parts II and III of this form and Form E01 (AUA Symptom Score Event Report).

C.2 Creatinine Rise Event

Record an 'X' in the corresponding box if the interim visit is scheduled to confirm a 50% increase in serum creatinine value from the baseline value (see patient label). Also complete parts II and III of this form and Form E02 (Creatinine Event Report).

C.3 Acute Urinary Retention Event

Record an 'X' in the corresponding box if the interim visit is scheduled to confirm an episode of acute urinary retention as defined by the protocol. Also complete parts II and III of this form and Form E03 (Urinary Event Report).

C.4 Recurrent Urinary Tract Infection Event

Record an 'X' in the corresponding box if the interim visit is scheduled to confirm recurrent urinary tract infection as defined by protocol. Also complete parts II and III of this form and Form E03 (Urinary Event Report).

C.5 Incontinence Event

Record an 'X' in the corresponding box if the interim visit is scheduled to confirm an incontinent event (defined by protocol as an involuntary loss of urine that is socially or hygienically unacceptable). Also complete parts II and III of this form and Form E03 (Urinary Event Report).

C.6 Adverse Event

Record an 'X' in the corresponding box if the interim visit is scheduled to confirm an adverse event. Also complete parts II and III of this form and Form E05 (Adverse Event Report) and Form E06 (Serious Adverse Event Report) if the event is serious.

C.7 Blood Pressure Management

Record an 'X' in the corresponding box if the interim visit is scheduled for blood pressure management. Also complete parts II and III of this form.

C.8 Dispense More Medication

Record an 'X' in the corresponding box if the interim visit is scheduled for the purpose of dispensing additional medication whether or not the patient is present (e.g. medication was mailed to the patient) or if the patient is dropping off or picking up his coded medication. Also complete parts II and III of this form ONLY.

C.9 Intercurrent Illness Event

Record an 'X' in the corresponding box if the interim visit is scheduled due to an intercurrent illness. This box should be checked if the patient is picking up medications for an intercurrent illness (e.g., caverjet, viagra, muse for impotence).

Also complete parts II, III and IV of this form. It also may be necessary to complete Form E05 (Adverse Event Report) and Form E06 (Serious Adverse Event Report).

An intercurrent illness is any event that is not related to the coded medications or progression of BPH that requires the discontinuation of coded medications.

C.10 TRUS and biopsy

Record an 'X' in the corresponding box if the interim visit is scheduled for the purpose of performing a TRUS with or without biopsy.

Also complete part III of this form ONLY.

C.11 Blood draw (other than creatinine rise)

Record an 'X' in the corresponding box if the interim visit is scheduled for the purpose of drawing blood for reasons other than for a creatinine rise.

Also complete part III of this form ONLY.

Section D - BLOOD PRESSURE READINGS

Refer to the *Blood Pressure Management Protocol* section in Chapter 6, page 1 for any questions regarding blood pressure.

D.1 Supine Blood Pressure (after patient is lying for 5 minutes)

D.1.a Blood Pressure

D.1.b Heart Rate

D.2 Standing Blood Pressure (immediately upon standing)

D.2.a Blood Pressure 1

D.2.b Heart Rate 1

After waiting 2 minutes

D.2.c Blood Pressure 2

D.2.d Heart Rate 2

Section E - ORTHOSTATIC HYPOTENSION

Refer to the *Orthostatic Hypotension* section in Chapter 6, page 2 for any questions.

E.1 Orthostatic Hypotension

If either D.2.a systolic or D.2.c systolic is 20 mmHg less than C.1.a systolic

OR if either D.2.a diastolic or D.2.c diastolic is 10 mmHg less than D.1.a diastolic

OR if the patient has developed significant postural hypotension, record YES.

Section F - Number of days since last visit

Refer to the patient's study calendar and count the days since the patient last attended a scheduled or interim follow-up visit.

Section G - DOXAZOSIN COMPLIANCE

Refer to the *Dispensing* section of the *Medical Therapy Protocol* section in Chapter 5, page 3 for any questions regarding doxazosin dispensing or compliance.

G.1 Dose of doxazosin

Record the appropriate dose of doxazosin currently being taken. If the patient is changing doses, record the dose the patient was taking until today's visit.

G.2 Number of doxazosin tablets dispensed at the last visit.

Record the number of doxazosin tablets dispensed at the last visit. Refer to the patient's dispensing record.

G.3 Number of doxazosin tablets returned today.

Record the number of tablets the patient returned today. Refer to the patient's dispensing record. If the patient does not return any tablets, regardless of the reason, the number of tablets returned is zero.

G.4 Compliance

Calculate compliance by the formula:

$$\frac{\text{tablets dispensed (G.2)} - \text{tablets returned (G.3)}}{\text{days since last dispensing visit (question F)}} \times 100$$

Record this value. Be sure to round to the nearest whole percentage.

There are 6 spaces to record compliance. This allows for compliance up to 999999% OR a negative compliance (5 digits with the negative sign). Therefore, unless any of the numbers used to calculate compliance are blank, compliance must be entered. PLEASE NOTE THAT THIS IS DIFFERENT FROM THE PILOT STUDY.

If the answer to G.4 is <80% compliance, counsel the patient.

G.5 Number of doxazosin tablets dispensed today.

Record the number of tablets dispensed today. Refer to the patient's dispensing record. Remove the label from the medication and place the label onto Form R03. If no medication was dispensed, then check the appropriate box on Form R03.

Affix the label from the doxazosin tablets dispensed today to the case report form.

Section H - FINASTERIDE COMPLIANCE

Refer to the *Dispensing* section of the *Medical Therapy Protocol* section in Chapter 5, page 3 for any questions regarding finasteride dispensing or compliance.

H.1 Number of finasteride tablets dispensed at the last visit.

Record the number of finasteride tablets dispensed at the last visit. Refer to the patient's dispensing record.

H.2 Number of finasteride tablets returned today.

Record the number of tablets the patient returned today. Refer to the patient's dispensing record. If the patient does not return any tablets, regardless of the reason, the number of tablets returned is zero.

H.3 Compliance

Calculate compliance by the formula:

$$\frac{\text{tablets dispensed (H.1)} - \text{tablets returned (H.2)}}{\text{days since last dispensing visit (question F)}} \times 100$$

Record this value. Be sure to round to the nearest whole percentage.

There are 6 spaces to record compliance. This allows for compliance up to 999999% OR a negative compliance (5 digits with the negative sign). Therefore, unless any of the numbers used to calculate compliance are blank, compliance must be entered. PLEASE NOTE THAT THIS IS DIFFERENT FROM THE PILOT STUDY.

If the answer to H.3 is <80% compliance, counsel the patient.

H.4 Number of finasteride tablets dispensed today.

Record the number of tablets dispensed today. Refer to the patient's dispensing record.

Remove the label from the medication and place the label onto Form R03. If no medication was dispensed, then check the appropriate box on Form R03.

Affix the label from the finasteride tablets dispensed today to the case report form.

Section I - CONCOMITANT MEDICATIONS

I.1. Is the patient currently taking coded doxazosin?

Record YES if patient is currently taking coded doxazosin. A patient currently taking doxazosin took the medication within 24 hours prior to the visit.

I.2. Is the patient currently taking coded finasteride?

Record YES if patient is currently taking coded finasteride. A patient currently taking finasteride took the medication within 24 hours prior to the visit.

I.3 Has the patient taken viagra (sildenafil citrate) since the last visit?

Record YES if the patient has taken viagra since his last scheduled or interim visit.

Section J - INTERCURRENT ILLNESS INFORMATION

Please note that an intercurrent illness is any event that is not related to the coded medications or progression of BPH that requires the discontinuation of coded medications.

J.1 Specify Intercurrent Illness

Record the illness.

J.2 Is this a Serious Event?

Record YES if the investigator has decided that the event is serious.

J.3 Specify action taken

Record any action taken with regard to the illness in question J.1.

J.4 Intercurrent Illness Event declared?

The investigator must consult the Clinical Review Committee, who will decide whether the event is serious enough to stop the coded medication.

If question J.4 is answered YES, complete question J.4.a. and the Principal Investigator must sign and date on the lines provided.

J.4.a Date of confirmation by Clinical Review Committee

If the medication is stopped, record the date that the Clinical Review Committee confirmed the stop point.

INSTRUCTIONS FOR COMPLETING FORM F04 - MISSED FOLLOW-UP VISIT REPORT

This form should be completed if a patient missed a titration visit or a scheduled follow-up visit and the appointment cannot be rescheduled within the 3 week visit window for quarterly visits, regardless of whether or not the patient is on abbreviated protocol. Any visits the patient attends after missing a visit and before the next scheduled visit are considered an Interim Visit (Form F03). If the clinic is notified ahead of time that the visit will be missed (including that the patient will be inactive or had died), a Form F04 must be completed for the first missed visit.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date follow-up visit was scheduled

Record the target date for the missed visit. Consult the patient's calendar for the target date of the scheduled visit that was missed.

B.2 Week of visit missed

Refer to the patient's study calendar and record the corresponding week number of the visit that was missed.

B.3 Type of visit missed

Record an 'X' in the box that corresponds to the type of visit missed.

B.4 Has there been any contact with the patient concerning his missed visit?

Record YES if the patient was contacted regarding the missed visit referred to in question B.1.

If question B.4 is answered YES, complete question B.4.a.

B.4.a In the coordinator's opinion, what is the primary reason for the missed visit?

Record the correct code for the primary reason for the missed visit.

Record an 'X' in the corresponding box, if the patient has moved to a location that makes follow-up too inconvenient. If the patient's new location is near another participating institution, contact the BCC for a possible transfer of records/follow-up.

Record an 'X' in the corresponding box, if illness, surgery or hospitalization is the primary reason for a missed visit. Form E05 (Adverse Event Report) **MUST** also be completed and Form E06 (Serious Adverse Event Report) if the event is serious.

Record an 'X' in the corresponding box, if general decline in motivation is the apparent cause of a missed visit. Employ appropriate positive counseling regarding importance of the study and to reinstall motivation. Make a notation to contact the patient prior to the next visit, reminding him of the upcoming appointment date and time; thus providing motivational support.

Record an 'X' in the corresponding box, if conflicting responsibilities are primary reason for a missed visit. Reschedule a visit at the earliest possible date.

Record an 'X' in the corresponding box, if the reason, in the opinion of the coordinator cannot be categorized

above. If question B.4.a is 'Other,' specify below.

B.4.a.i Specify the reason for the missed visit.

B.5. Is the patient considered to be inactive (discontinued follow-up visits)?

Record YES if the patient has discontinued follow-up visits and should be considered as inactive.

INSTRUCTIONS FOR COMPLETING FORM F06 - TITRATION VISIT INVENTORY

This form should be completed at End Week 3 and End Week 4 of any titration period.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of Visit

Record the date the patient attends the follow-up visit.

B.2 Week of Visit

Refer to the patient's study calendar and record the week number that corresponds to the date in Question B.1.

Section C - BLOOD PRESSURE READINGS

Refer to the *Blood Pressure Management Protocol* section in Chapter 6, page 1 for any questions regarding blood pressure.

C.1 Supine Blood Pressure (after patient is lying for 5 minutes)

C.1.a Blood Pressure

C.1.b Heart Rate

C.2 Standing Blood Pressure (immediately upon standing)

C.2.a Blood Pressure 1

C.2.b Heart Rate 1

After waiting 2 minutes

C.2.c Blood Pressure 2

C.2.d Heart Rate 2

Section D - ORTHOSTATIC HYPOTENSION

Refer to the *Orthostatic Hypotension* section in Chapter 6, page 2 for any questions.

D.1 Orthostatic Hypotension

If either C.2.a systolic or C.2.c systolic is 20 mmHg less than C.1.a systolic

OR if either C.2.a diastolic or C.2.c diastolic is 10 mmHg less than C.1.a diastolic

OR if the patient has developed significant postural hypotension, record YES.

Section E - Number of Days Since Last Visit

Refer to the patient's study calendar and count the days since the patient last attended a scheduled or interim follow-up visit.

Section F - DOXAZOSIN COMPLIANCE

Refer to the *Dispensing* section of the *Medical Therapy Protocol* section in Chapter 5, page 3 for any questions regarding doxazosin dispensing or compliance.

F.1 Dose of doxazosin

Record the appropriate dose of doxazosin currently being taken. If the patient is changing doses, record the dose the patient was taking until today's visit.

F.2 Number of doxazosin tablets dispensed at the last visit

Record the number of doxazosin tablets dispensed at the last visit (scheduled or interim). Refer to the patient's dispensing record.

F.3 Number of doxazosin tablets returned today

Record the number of tablets the patient returned today. Refer to the patient's dispensing record. If the patient does not return any tablets, regardless of the reason, the number of tablets returned is zero.

F.4 Compliance

Calculate compliance by the formula:

$$\frac{\text{tablets dispensed (F.2)} - \text{tablets returned (F.3)}}{\text{days since last dispensing visit (question E)}} \times 100$$

Record this value. Be sure to round to the nearest whole percentage.

There are 6 spaces to record compliance. This allows for compliance up to 999999% OR a negative compliance (5 digits with the negative sign). Therefore, unless any of the numbers used to calculate compliance are blank, compliance must be entered. PLEASE NOTE THAT THIS IS DIFFERENT FROM THE PILOT STUDY.

If the answer to question F.4 is <80% compliance, counsel the patient.

F.5 Number of doxazosin tablets dispensed today

Record the number of tablets dispensed today. Refer to the patient's dispensing record.

Remove the label from the medication and place the label onto Form R03. If no medication was dispensed, then check the appropriate box on Form R03.

Affix the label from the doxazosin tablets dispensed today to Form R03.

Section G - FINASTERIDE COMPLIANCE

Refer to the *Dispensing* section of the *Medical Therapy Protocol* section in Chapter 5, page 3 for any questions regarding finasteride dispensing or compliance.

G.1 Number of finasteride tablets dispensed at the last visit

Record the number of finasteride tablets dispensed at the last visit (scheduled or interim). Refer to the patient's dispensing record.

G.2 Number of finasteride tablets returned today

Record the number of tablets the patient returned today. Refer to the patient's dispensing record. If the patient does not return any tablets, regardless of the reason, the number of tablets returned is zero.

G.3 Compliance

Calculate compliance by the formula:

$$\frac{\text{tablets dispensed (G.2)} - \text{tablets returned (G.3)}}{\text{days since last dispensing visit (question E)}} \times 100$$

Record this value. Be sure to round to the nearest whole percentage.

There are 6 spaces to record compliance. This allows for compliance up to 999999% OR a negative compliance (5 digits with the negative sign). Therefore, unless any of the numbers used to calculate compliance are blank, compliance must be entered. PLEASE NOTE THAT THIS IS DIFFERENT FROM THE PILOT STUDY.

If the answer to question G.4 is <80% compliance, counsel the patient.

G.4 Number of finasteride tablets dispensed today

Record the number of tablets dispensed today. Refer to the patient's dispensing record.

Remove the label from the medication and place the label onto Form R03. If no medication was dispensed, then check the appropriate box on Form R03.

Affix the label from the finasteride tablets dispensed today to Form R03.

Section H - CONCOMITANT MEDICATIONS

H.1 Is the patient taking coded doxazosin?

Record YES if the patient is currently taking coded doxazosin. A patient currently taking doxazosin took the medication within 24 hours prior to the visit.

H.2 Is the patient taking the coded finasteride?

Record YES if the patient is currently taking coded finasteride. A patient currently taking finasteride took the medication within 24 hours prior to the visit.

H.3 Is the patient taking any medication other than the coded medications?

Record YES if the patient is taking any medication other than the coded medications today. Remember this is a "snap-shot" of medications; just record the medications being taken today (NOT all medications taken since last visit).

If Question H.3 is answered YES, complete question H.3.a-j.

H.3.a-j List all medications, consulting PDR for spelling and *Exclusionary Medication* section (Chapter 6, page 3) for excluded medications.

Refer to the Concomitant Medication Dictionary for the proper recording of names and form of concomitant medications.

H.4 Has the patient taken viagra (sildenafil citrate) since the last visit?

Record YES if the patient has taken viagra since his last scheduled or interim visit.

Section I - ADVERSE EVENTS

Refer to the *Clinical Events Protocol* section in Chapter 6, page 6 for any questions regarding adverse events and how to report them.

I.1 Since the last scheduled follow-up visit, has the patient had any adverse experiences, drug reactions, side effects, abnormal laboratory values, hospitalizations, other complications or pre-existing conditions that worsened?

Laboratory changes include those values considered to be out of normal range, that are clinically significant (as determined by a physician) or those not immediately explainable.

Adverse events are not intended to include the fluctuation of symptoms associated with bladder outlet obstruction (BPH). This information is captured on CRFs, but are not considered to be adverse events unless they seem unusual or unexplainable. If this question is answered YES, also complete Form E05 (Adverse Event Report) and Form E06 (Serious Adverse Event Report) if the event is serious.

INSTRUCTIONS FOR COMPLETING FORM F07 - POST END-OF-STUDY VISIT INVENTORY

This form should be completed at any visit that takes place after the end-of-study visit. Separation visits will be scheduled for all patients who attend an end-of-study visit whether or not they are continuing on coded medications.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of Visit

Record the date the patient attends the follow-up visit.

B.2 Week of Visit

Refer to the patient's study calendar and record the week number that corresponds to the date in Question B.1.

B.3 Type of Visit

Record an 'X' in the box that corresponds to the type of visit.

If this is a Follow-up Visit, CONTINUE.

If this is a Separation Visit, SKIP to section E.

Section C - BLOOD PRESSURE READINGS

Refer to the *Blood Pressure Management Protocol* section in Chapter 6, page 1 for any questions regarding blood pressure.

C.1 Supine Blood Pressure (after patient is lying for 5 minutes)

C.1.a Blood Pressure

C.1.b Heart Rate

C.2 Standing Blood Pressure (immediately upon standing)

C.2.a Blood Pressure 1

C.2.b Heart Rate 1

After waiting 2 minutes

C.2.c Blood Pressure 2

C.2.d Heart Rate 2

Section D - ORTHOSTATIC HYPOTENSION

Refer to the *Orthostatic Hypotension* section in Chapter 6, page 2 for any questions.

D.1 Orthostatic Hypotension

If either standing systolic (question C.2.a or C.2.c) is 20 mmHg less than the supine systolic (question C.1.a)

OR if either standing diastolic (question C.2.a or C.2.c) is 10 mmHg less than the supine diastolic (question C.1.a)

OR if the patient has developed significant postural hypotension, record YES.

Section E - GENERAL MEDICATION DISPENSING INFORMATION

E.1 Is the patient currently taking coded doxazosin?

Record YES if the patient is currently taking coded doxazosin. A patient currently taking doxazosin took the medication within 24 hours prior to the visit.

E.2 Is the patient currently taking the coded finasteride?

Record YES if the patient is currently taking coded finasteride. A patient currently taking finasteride took the medication within 24 hours prior to the visit.

If either question E.1 or E.2 is answered YES, CONTINUE.

If both question E.1 and E.2 are answered NO, SKIP to section J.

E.3 Number of days since last visit

Refer to the patient's study calendar and count the days since the patient last attended a scheduled or interim visit.

Section F - DOXAZOSIN COMPLIANCE

Refer to the *Dispensing* section of the *Medical Therapy Protocol* section in Chapter 5, page 3 for any questions regarding doxazosin dispensing or compliance.

F.1 Dose of doxazosin

Record the appropriate dose of doxazosin currently being taken. If the patient is changing doses, record the dose the patient was taking until today's visit.

F.2 Number of doxazosin tablets dispensed at the last visit

Record the number of doxazosin tablets dispensed at the last visit (scheduled or interim). Refer to the patient's dispensing record.

F.3 Number of doxazosin tablets returned today

Record the number of tablets the patient returned today. Refer to the patient's dispensing record. If the patient does not return any tablets, regardless of the reason, the number of tablets returned is zero.

F.4 Compliance

Calculate compliance by the formula:

$$\frac{\text{tablets dispensed (F.2) - tablets returned (F.3)}}{\text{days since last dispensing visit (question E)}} \times 100$$

Record this value. Be sure to round to the nearest whole percentage.

There are 6 spaces to record compliance. This allows for compliance up to 999999% OR a negative compliance (5 digits with the negative sign). Therefore, unless any of the numbers used to calculate compliance are blank, compliance must be entered. PLEASE NOTE THAT THIS IS DIFFERENT FROM THE PILOT STUDY.

If you answer question F.4 is <80% compliance, counsel the patient.

F.5 Number of doxazosin tablets dispensed today

Record the number of tablets dispensed today. Refer to the patient's dispensing record.

Affix the label from the doxazosin tablets dispensed today to the appropriate page of Form R03.

Section G - FINASTERIDE COMPLIANCE

Refer to the *Dispensing* section of the *Medical Therapy Protocol* section in Chapter 5, page 3 for any questions regarding finasteride dispensing or compliance.

G.1 Number of finasteride tablets dispensed at the last visit

Record the number of finasteride tablets dispensed at the last visit (scheduled or interim). Refer to the patient's dispensing record.

G.2 Number of finasteride tablets returned today

Record the number of tablets the patient returned today. Refer to the patient's dispensing record. If the patient does not return any tablets, regardless of the reason, the number of tablets returned is zero.

G.3 Compliance

Calculate compliance by the formula:

$$\frac{\text{tablets dispensed (G.2)} - \text{tablets returned (G.3)}}{\text{days since last dispensing visit (question E)}} \times 100$$

Record this value. Be sure to round to the nearest whole percentage.

There are 6 spaces to record compliance. This allows for compliance up to 999999% OR a negative compliance (5 digits with the negative sign). Therefore, unless any of the numbers used to calculate compliance are blank, compliance must be entered. PLEASE NOTE THAT THIS IS DIFFERENT FROM THE PILOT STUDY.

If the answer to question G.4 is <80% compliance, counsel the patient.

G.4 Number of finasteride tablets dispensed today

Record the number of tablets dispensed today. Refer to the patient's dispensing record.

Affix the label from the finasteride tablets dispensed today to the appropriate page of Form R03.

Section H - CONCOMITANT MEDICATIONS

H.1 Is the patient currently taking any medication other than the coded medications?

Record YES if the patient is taking any medication other than the coded medications today. Remember this is a "snap-shot" of medications; just record the medications being taken today (NOT all medications taken since last visit).

If Question H.3 is answered YES, complete question H.3.a-j.

H.1.a-j List all medications, consulting PDR for spelling and *Exclusionary Medication* section (Chapter 6, page 3)

for excluded medications.

Refer to the Concomitant Medication Dictionary for the proper recording of names and form of concomitant medications.

H.2 Has the patient taken viagra (sildenafil citrate) since the last visit?

Record YES if the patient has taken viagra since his last scheduled or interim visit.

Section I - ADVERSE EVENTS

Refer to the *Adverse Event Reporting* section in Chapter 4, page ? for any questions regarding adverse events and how to report them.

I.1 Since the last scheduled follow-up visit, has the patient had any adverse experiences, drug reactions, side effects, abnormal laboratory values, hospitalizations, other complications or pre-existing conditions that worsened?

Please ask the patient about Adverse Events using the wording on the form, so as not to bias his answer.

Laboratory changes include those values considered to be out of normal range, that are clinically significant (as determined by a physician) or those not immediately explainable.

Adverse events are not intended to include the fluctuation of symptoms associated with bladder outlet obstruction (BPH). This information is captured on CRFs, but are not considered to be adverse events unless they seem unusual or unexplainable. If this question is answered YES, also complete Form E05 (Adverse Event Report) and if necessary, Form E06 (Serious Adverse Event Report).

If this is a separation visit, CONTINUE.

Section J - TREATMENT GROUP DISCLOSURE

For all patients the treatment group assignment should be obtained from the MTOPS staff website or study computer.

J.1 Was the patient informed of his treatment group assignment?

Record YES if clinic staff informed the patient of his treatment group assignment.

J.1.a Treatment group assignment disclosed to patient

Record an 'X' in the appropriate box that corresponds to the treatment group assignment disclosed to the patient.

INSTRUCTIONS FOR COMPLETING FORM P01 - TRUS AND BIOPSY INFORMATION

This form is completed when the TRUS is performed at Screening Visit 2 and End of Study, with or without biopsy. For patients participating in the biopsy substudy, it is also completed at the 12-month Standard Follow-up Visit. If a patient reaches a primary endpoint, an additional biopsy will be performed at confirmation of the event. If a patient is due to have a biopsy at any of the aforementioned time points, it need not be repeated if a biopsy was performed within the prior three months. All biopsies performed for patients in the biopsy substudy should be performed using study protocol with tissue sent through the Diagnostic Center. It is important that all other procedures and questionnaires are completed before a biopsy is performed. Refer to the *Transrectal Ultrasound of the Prostate* section in Chapter 7, page 6 and the *Biopsy* section in Chapter 7, page 9 for any questions regarding these procedures.

Section A- IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of Visit

Record the date the TRUS and biopsy procedures were performed.

B.2 Type of Visit

Record an 'X' in the corresponding box for the type of visit.

B.3 If Follow-up Visit, week of visit

Refer to the patient's study calendar and record the week number that corresponds to the date in question B.1.

B.4 Sonologist's Initials

Record the first two letters of the sonologist's first name and the first two letters of their last name. It is very important to always use the same initials for each sonologist, (i.e. someone named James (JA) and called Jim (JI) could have different initials).

B.5 Type of Ultrasound Equipment

Record an 'X' in the box that corresponds to the type of ultrasound equipment used.

B.5.a. If other, specify the type of ultrasound equipment used.

If the ultrasound equipment used was not Bruel & Kjaer or Dornier, record the type of equipment used.

Section C - MAILING INFORMATION

Refer to the *Anatomic Pathology* section in Chapter 8, page 1 for any questions regarding tissue biopsy tissue preparation and mailing.

C.1 Was at least one biopsy performed?

Record YES if at least one biopsy was performed.

Record NO if no biopsies were performed.

If question C.1 is answered YES, complete question C.1.a.

If question C.1 is answered NO, Skip to Section D and DO NOT complete Section E (Concomitant Medications)

C.1.a Date tissue sent to the Diagnostic Center.

Record the date the biopsy tissue was sent to the Diagnostic Center.

Section D - ULTRASOUND MEASUREMENTS

It is very important to inform the sonologist of the measurements that are required for this study as these measurements may not be standard at all facilities. It may be helpful to copy the page(s) of the case report form to give to the sonologist as a guideline.

D.1 Total Gland

D.1.a Transverse View

D.1.a.i Height

D.1.a.ii Width

D.1.b Longitudinal View

D.1.b.i Height

D.1.b.ii Length

D.1.c Ellipsoid Volume

Record the Ellipsoid Volume as read by the machine.

D.2 Transition Zone

D.2.a Transverse View

D.2.a.i Height

D.2.a.ii Width

D.2.b Longitudinal View

D.2.b.i Height

D.2.b.ii Length

D.2.c Ellipsoid Volume

Record the Ellipsoid Volume as read by the machine.

For questions D.3 - D.6, check all responses that apply. Any one of these questions may be left blank.

D.3 Inner Gland

D.4 Peripheral Zone

D.5 Surgical Capsule

D.6 Capsule

Section E - CONCOMITANT MEDICATIONS

E.1 Is the patient currently taking any medication other than the coded medications?

Record YES if patient is taking any medication other than coded medications today. Remember this is a "snapshot" of medications; record the medications being taken today (NOT all medications taken since last visit). This listing should include any prophylactic medications prescribed for the biopsy procedure.

E.1.a-j. If YES, list below.

List all medications, consulting PDR for spelling and *Exclusionary Medications* section (Chapter 6, page 3) for excluded medications.

Refer to the Concomitant Medication Dictionary for the proper recording of names and form of concomitant medications.

E.2 Has the patient taken viagra (sildenafil citrate) since the last visit?

Record YES if the patient has taken viagra since his last scheduled or interim visit.

INSTRUCTIONS FOR COMPLETING FORM P04 - NON-SCHEDULED BIOPSY INFORMATION

This form is completed any time after randomization that a biopsy is performed that is for a patient who is not participating in the biopsy substudy or for a patient who is participating in the biopsy substudy, but the biopsy was performed outside the study (tissue was NOT processed by the Diagnostic Center). This form should also be completed for invasive therapy procedures that entail pathology reports for prostate tissue taken.

Note: If a patient did not sign a informed consent to be in the biopsy substudy and thus did not have a biopsy at baseline, follow-up biopsies for this patient should not be performed using study protocol with tissue sent to the Diagnostic Center. If a patient who is not in the biopsy substudy requires a biopsy after randomization, the biopsy should be performed outside of the study and this form should be completed.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of procedure

Record the date the procedure was performed.

B.2 Week of visit

Refer to the patient's study calendar and record the week number that corresponds to the date in question B.1.

B.3 Is the pathology information from a TRUS/biopsy (not an invasive therapy)?

Record YES if the pathology information is from a TRUS/biopsy.

If YES, continue. If NO, SKIP to question C.2.

B.4 Sonographer's Initials

Record the first two letters of the sonographer's first name and the first two letters of their last name. It is very important to always use the same initials for each sonographer, (i.e. someone named James (JA) and called Jim (JI) could have different initials).

B.5 Reason for Biopsy

Record an 'X' in the box that corresponds to the reason that the biopsy was performed. If the reason for the biopsy is other than those listed, specify the reason for the biopsy.

Section C - Biopsy Information and Results

The information in this section should be obtained from the local pathology report, a copy of which should be attached to this form.

C.1 Number of cores obtained

Specify the number of cores obtained for the biopsy.

C.2 Biopsy Results

Check all responses that apply to the results obtained from the local pathology report.

If question C.2 is answered Cancer, complete question C.2.a.

If question C.2 is answered Dysplasia/PIN, complete question C.2.b.

C.2.a. Cancer

C.2.a. I. Primary Gleason Score

Record the Primary Gleason Score recorded on the local pathology report.

C.2.a. ii. Secondary Gleason Score

Record the Secondary Gleason Score recorded on the local pathology report.

C.2.a. iii. Gleason Sum

Record the Gleason Sum recorded on the local pathology report. If the sum is not recorded, it can be obtained by summing the Primary Gleason Score and the Secondary Gleason Score.

C.2.b. Dysplasia/PIN

C.2.b. I. Grade

Record an 'X' in the box that corresponds to the grade recorded on the local pathology report.

C.3 Is a copy of the pathology report attached?

Record an 'X' in the box that corresponds to whether a copy of the pathology report is attached.

If question C.3 is answered NO, complete question C.3.a.

C.3.a. Why not?

A copy of the local biopsy report should be attached. If the biopsy report is not attached, please provide a short explanation.

INSTRUCTIONS FOR COMPLETING FORM Q01 - AUA SYMPTOM QUESTIONNAIRE

This form is to be completed at every scheduled visit (not at interim visits unless the interim visit is for an AUA Symptom Score event).

If the patient is more comfortable with written Spanish, then he should complete the Spanish version. If the patient cannot read English or Spanish, then the questionnaire may be administered verbally (as an interview version would be given). In all cases, whichever version is used at Screening Visit 1 must be used throughout the study.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of visit

Record the date the patient attends the visit. This date should be the same as the date on the other forms completed for the visit.

B.2 Type of visit

Record an 'X' in the box that corresponds to the type of visit missed.

B.3 If follow-up or End of Study visit, week of visit

Refer to the patient's study calendar and record the week number that corresponds to the date in question B.1.

Part II / SYMPTOM SCORE QUESTIONNAIRE

Sections A, B, C

The patient should complete the questionnaire to the best of his capability. Please check the patient's answers to insure that they are legible. It is a good practice to add up the Symptom Score while the patient is still available, so that any problems can be rectified. This will force the coordinator to review the patient's answers for double answers, missed answers, etc. All questions in Part II section A and B must be answered in order to tabulate a valid symptom score. If a patient indicates more than one answer for a question or missed answers, the symptom score cannot be tabulated. If the patient changes an answer on a question, he should be instructed to put his initials next to the question, thereby acknowledging that he made the correction.

If this visit is Screening Visit 1 OR 2, the AUA symptom score (Part A) must be ≥ 8 AND ≤ 30 or the patient is ineligible. All questions on the AUA Symptom Score must be answered. See Form B01 (Eligibility and Exclusion Inventory), question C.4.

INSTRUCTIONS FOR COMPLETING FORM Q02 - SEXUAL FUNCTION QUESTIONNAIRE

This form should be completed at Screening Visit 1. Prior to introducing the sexual function questionnaire, the coordinator should inform the patient that this information is sensitive and personal. It is advisable for the patient to complete this questionnaire in privacy.

The patient may refuse to complete the form at any time, including during screening. If the patient refuses during screening, the patient is still eligible for randomization. In any case, no portion of Form Q02 should be completed, not even the ID information on page one. The patient notes should include that the patient refused.

If the patient is more comfortable with written Spanish, then he should complete the Spanish version. If the patient cannot read English or Spanish, then the questionnaire may be administered verbally (as an interview version would be given). In all cases, whichever version is used at Screening Visit 1 must be used throughout the study.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of visit

Record the date the patient attends the visit. This date should be the same as the date on the other forms completed for the visit.

B.2 Type of visit

Record an 'X' in the box that corresponds to the type of visit.

B.3 If Standard or Major follow-up visit, week of visit

Refer to the patient's study calendar and record the week number that corresponds to the date in question B.1.

Part II / SEXUAL FUNCTION QUESTIONNAIRE

The patient should complete the questionnaire to the best of his capability. Please check the patient's answers to insure that they are legible and that there are no double answers or missed answers. It is a good practice to review the questionnaire while the patient is still available, so that any problems can be rectified. If the patient changes an answer on a question, he should be instructed to put his initials next to the question, thereby acknowledging that he made the correction.

INSTRUCTIONS FOR COMPLETING FORM Q03 - HEALTH SURVEY QUESTIONNAIRE

This form is to be completed at Screening Visit 2, Major Follow-up Visits, and End of Study Visit.

If the patient is more comfortable with written Spanish, then he should complete the Spanish version. If the patient cannot read English or Spanish, then the interview version of the questionnaire should be administered verbally. In all cases, whichever version is used at Screening Visit 2 must be used throughout the study.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of visit

Record the date the patient attends the visit. This date should be the same as the date on the other forms completed for the visit.

B.2 Type of visit

Record an 'X' in the box that corresponds to the type of visit.

B.3 If follow-up or End of Study visit, week of visit

Refer to the patient's study calendar and record the week number that corresponds to the date in question B.1.

B.4 Type of questionnaire

Record an 'X' in the box that corresponds to the type of questionnaire. This question will not be entered into the microcomputer.

Part II / HEALTH SURVEY QUESTIONNAIRE

Sections A, B, C

The patient should complete the questionnaire to the best of his capability. Please check the patient's answers to insure that they are legible. It is a good practice to do this while the patient is still available, so that any problems can be rectified. This will force the coordinator to review the patient's answers for double answers, missed answers, etc. If the patient changes an answer on a question, he should be instructed to put his initials next to the question, thereby acknowledging that he made the correction.

INSTRUCTIONS FOR COMPLETING FORM Q04 - PROSTATITIS QUESTIONNAIRE

This form is to be completed at Screening Visit 2, Major Follow-up Visits and End of Study.

If the patient is more comfortable with written Spanish, then he should complete the Spanish version. If the patient cannot read English or Spanish, then the questionnaire may be administered verbally (as an interview version would be given). In all cases, whichever version is used at Screening Visit 1 must be used throughout the study.

Part I - IDENTIFICATION

Section A - Patient Identification

A.1 - A.4 See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - Visit Information

B.1 Date of visit

Record the date the questionnaire is being completed.

B.2 Type of visit

Record an 'X' in the appropriate box.

B.3 If follow-up or End-of Study Visit, week of visit

Refer to the patient's study calendar and record the week number that corresponds to the date in question B.1.

Part II - PROSTATITIS QUESTIONNAIRE

The patient should complete the questionnaire to the best of his capability. Please check the patient's answers to insure that they are legible and that there are no double answers or missed answers. It is a good practice to review the questionnaire while the patient is still available, so that any problems can be rectified. If the patient changes an answer on a question, he should be instructed to put his initials next to the question, thereby acknowledging that he made the correction.

INSTRUCTIONS FOR COMPLETING FORM R01 - CLINICAL LABORATORY NORMAL RANGE REPORT

The purpose of this form is to document, over the course of the trial, the "normal range of values" from a clinic's laboratory tests listed on the Screening Visit 1 Inventory (Form B02) and Major Follow-up Visit Inventory (Form F02). The information will be used to conduct statistical analyses of the study's laboratory measurements relative to the clinic laboratories test-specific normal range (i.e., "percent of normal" analysis). If there is more than one laboratory being used in the study, a form should be completed for each laboratory.

The original of this form is to be returned to the BCC. Retain a copy in the clinic files.

To help document any changes in the "normal range of values" occurring during the study period, a new Clinic Laboratory Normal Range Report (Form R01) should be completed any time the laboratory changes a normal range. Changes do not need to be sent to the BCC -- only the microcomputer should be updated with the date of the change and the new normal range.

If for any range, the normal is < some value, record this as from "0" to that value.
Take care to convert the value to the units on the case report form when necessary.

Section A - CLINIC IDENTIFICATION

A.1 Clinic Number

Record the appropriate clinic number in the boxes provided. The clinic number is provided in the MTOPS Directory of Participants.

A.2 Laboratory Code

Complete this question ONLY if the clinic is using more than one laboratory. Please call the BCC to establish

laboratory codes.

A.3 If not initial report, date of change

Record the date the change in initial value was implemented. Do not complete this question for the initial report. If completing a Form R01 to make a change - only complete the ranges that changed, others may be left blank.

Section B - COMPLETE BLOOD COUNT NORMAL RANGES

B.1 Leucocyte Count (WBC)

Record the range in $10^3/\text{ul}$.

B.2 Erythrocyte Count (RBC)

Record the range in $10^6/\text{ul}$.

B.3 Hemoglobin

Record the range in g/dl.

B.4 Hematocrit

Record the range as a percentage (%).

B.5 Platelet Count

Record the range in $10^3/\text{ul}$.

Section C - SERUM CHEMISTRIES NORMAL RANGES

C.1 Sodium

Record the range in mmol/L.

C.2 Potassium

Record the range in mmol/L.

C.3 Chloride

Record the range in mmol/L.

C.4 Bicarbonate

Record the range in mEq/L.

C.5 Glucose

Record the range in mg/dl.

C.6 Urea Nitrogen

Record the range in mg/dl.

C.7 Creatinine

Record the range in mg/dl.

C.8 Uric Acid

Record the range in mg/dl.

C.9 Calcium

Record the range in mg/dl.

C.10 Phosphorus

Record the range in mg/dl.

C.11 ALT (SGPT)

Record the range in U/L.

C.12 Alkaline Phosphatase

Record the range in U/L.

C.13 Total Bilirubin

Record the range in mg/dl.

C.14 Total Protein

Record the range in g/dl.

C.15 Albumin

Record the range in g/dl.

C.16 Cholesterol

Record the range in mg/dl.

INSTRUCTIONS FOR COMPLETING FORM R03 - DISPENSE LABEL REPORT

This form is to be completed during the Medication Run-in Period, Titration, Quarterly Visits, and Interim Visits. Remove the label from all coded medication before dispensing and affix it to the appropriate area on the specific Form R03.

Medications from the Medication Run-in Period should be affixed to the Medication Run-in Form.

Medications from the Titration should be affixed to the Titration Form. If medication was not dispensed during this visit, then check the appropriate box.

Medications from the Quarterly Visit should be affixed to the Quarterly Visit Form. If medication was not dispensed during this visit, then check the appropriate box.

Medications from the Interim Visit should be affixed to the Interim Visit Form. If medication was not dispensed during this visit, then check the appropriate box.

INSTRUCTIONS FOR COMPLETING FORM R06 - MISSED BIOPSY REPORT

This form should be completed for a patient in the biopsy substudy on active follow-up, any time after randomization that a biopsy should be performed but is not performed. These visits are end-year 1 visit, primary endpoint declaration and end-of-study. Biopsies need not be performed if the patient has been diagnosed with prostate cancer, has crossed over to known invasive therapy or has had a biopsy within 3 months prior to the visit.

Section A - PATIENT IDENTIFICATION

A.1 - A.3 See Instructions for completing Patient Identification on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of follow-up visit

Record the target date of the patient's missed follow-up visit.

B.2 Week of visit

Refer to the patient's study calendar and record the week number that corresponds to the date in Question B.1.

B.3 Type of visit

Record an 'X' in the corresponding box for the type of visit.

B.4 Reason biopsy was not performed

Record the reason why the biopsy was not performed.

INSTRUCTIONS FOR COMPLETING FORM R07 - PSA COLLECTION REPORT

This form should be completed any time after randomization that serum specimen is collected for Diagnostic Center determination of PSA.

Note: For a participant who has rechallenged coded finasteride within the last 3 months, PSA draw should be postponed until 3 months have elapsed although it is not required.

Note: After this form is entered and transmitted to the BCC, questions B.4 and B.4a cannot be changed. Therefore, all information should be verified before entering the form into the clinic computer.

Section A - PATIENT IDENTIFICATION

A.1 - A.3 See Instructions for completing Patient Identification on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date serum specimen collected

Record the date the serum specimen was collected.

B.2 Week of visit

Refer to the patient's study calendar and record the week number that corresponds to the date in Question B.1.

B.3 Type of visit

Record an 'X' in the corresponding box for the type of visit.

If Interim, Standard Follow-up or Titration Visit, CONTINUE.

If Major Follow-up Visit, SKIP to Question B.4

B.3a Reason for collection

Record the reason why the serum specimen was collected.

B.4 Has the patient been off coded finasteride for at least 16 weeks?

Record YES if the patient has not taken coded finasteride in the past 16 weeks.

If YES, CONTINUE.

B.4a Date coded finasteride discontinued

Record the date that coded finasteride was discontinued.

INSTRUCTIONS FOR COMPLETING FORM R08 - PROSTATE CANCER REGISTRY REPORT

This form should be completed for any randomized patient diagnosed with prostate cancer. A copy of the completed form (including attachments) should be sent to the BCC. Any personal identification information should be blacked out on the copy of the attachments sent to the BCC.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of Visit

Record the date the patient attends the follow-up visit.

B.2 Reason for biopsy

Record an 'X' in the box that corresponds to the reason for the biopsy. More than one box may be checked.

Section C - BIOPSY INFORMATION AND REPORTS

C.1 Was the biopsy performed and sent to the Diagnostic Center for analysis and banking by the MTOPS biopsy substudy protocol?

Record YES if the biopsy tissue was sent to the Diagnostic Center for analysis and banking by the MTOPS biopsy substudy protocol.

If YES, STOP. If NO, then CONTINUE.

C.1.a Was Form P04 (Non-Scheduled Biopsy Information) completed?

Record YES if Form P04 has been completed. If NO, Form P04 should be completed at this time.

C.1.b Was a TRUS performed with the biopsy?

Record YES if a TRUS was performed with the biopsy.

If YES:

C.1.b.i Is the ultrasound report attached?

Record YES if the ultrasound report is attached.

If NO:

C.1.b.i.a Why not?

Record the reason why the ultrasound report is not attached. Please note, all means possible

should be used to obtain this report. Once the report is located, it must be copied and attached to this CRF.

INSTRUCTIONS FOR COMPLETING FORM R09 - PRIOR USE OF VIAGRA REPORT

This form should be completed one time for each randomized patient at the first follow-up visit after January 1, 2000 to document the usage of viagra in the past.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of Visit

Record the date the patient attends the follow-up visit.

Section C - VIAGRA USE INFORMATION

C.1 Has the patient taken viagra any time in the past?

Record YES if the patient has taken viagra any time in the past.

If YES, continue.

C.1.a Is this the first time viagra use is documented on a CRF?

Record YES if this is the first time viagra use is documented on a CRF.

INSTRUCTIONS FOR COMPLETING FORM R10 - FINAL STATUS REPORT FOR INACTIVE PATIENTS

This form is completed for all patients who are inactive prior to death or the administrative censoring date of November 30, 2001. The purpose of this form is to document the final status of the aforementioned patients as of November 30, 2001.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - LAST VISIT INFORMATION

The last completed follow-up visit includes all visits that the patient attended in person (i.e., this does not include Interim Visits for which medications were mailed).

B.1 Date of last completed follow-up visit

Record the date of the last completed follow-up visit.

B.2 Specify the classification of this patient at the last completed follow-up visit.

Record an 'X' in all applicable boxes that correspond to the classification of this patient. If any of these events have occurred, skip the section listed. At the last completed follow-up visit, if none of the listed events have occurred, check "none of the above". If this box is checked, all sections of this form must be completed.

Section C - OPEN-LABEL MEDICATION STATUS

This section should be completed if an 'X' was NOT marked in question B.2, initiated open-label medication.

C.1 Did the patient initiate open-label medication since the last completed follow-up visit?

Record YES if the patient initiated any type of open-label medication since his last completed visit. This includes, but is not limited to, all α -1 blockers, all 5- α reductase inhibitors and all hormonal therapy.

If NO or Unknown, SKIP to Section D, if applicable.

If YES, CONTINUE.

Please answer the following questions for the first dispensing of open-label medications only.

C.1.a Specify the medical therapy:

Record an 'X' in the box that corresponds to the type of medical therapy initiated. More than one box may be checked.

C.1.b Date of open-label medications dispensed

Record the date open-label medications were dispensed.

Section D - CROSSOVER TO INVASIVE THERAPY STATUS

This section should be completed if an 'X' was NOT marked in question B.2, crossed over to invasive therapy.

D.1 Did the patient cross over to invasive therapy since the last completed follow-up visit?

Record YES if the patient crossed over to invasive therapy since his last completed visit.

If NO or Unknown, SKIP to Section E, if applicable.

If YES, CONTINUE.

Please answer the following questions for the first invasive therapy performed.

D.1.a Specify the invasive therapy:

Record an 'X' in the box that corresponds to the type of invasive therapy performed.

D.1.b Date of crossover to invasive therapy

Record the date invasive therapy was performed.

Section E - PROSTATE CANCER STATUS

This section should be completed if an 'X' was NOT marked in question B.2, diagnosis of prostate cancer.

E.1 Has the patient been diagnosed with prostate cancer since the last completed follow-up visit?

Record YES if the patient has been diagnosed with prostate cancer since his last completed visit.

If YES, CONTINUE.

If NO or Unknown, SKIP to Section F.

E.1.a Date of cancer diagnosis

Record the date of cancer diagnosis.

E.1.b Did the patient undergo an invasive therapy after diagnosis of prostate cancer that was not captured in

Section D?

Record YES if invasive therapy was performed after the cancer diagnosis and is not captured in section D.

If NO or Unknown, SKIP to Section F, if applicable.

If YES, CONTINUE.

E.1.b.i Specify the invasive therapy:

Record an 'X' in the box that corresponds to the type of invasive therapy performed.

E.1.b.ii Date of crossover to invasive therapy

Record the date invasive therapy was performed.

Section F - BLADDER CANCER STATUS

This section should be completed if an 'X' was NOT marked in question B.2, diagnosis of bladder cancer.

F.1 Has the patient been diagnosed with bladder cancer since the last completed follow-up visit?

Record YES if the patient has been diagnosed with bladder cancer since his last completed visit.

If question F.1 is answered YES, CONTINUE.

If question F.1 is answered NO or Unknown, SKIP to Section G.

F.1.a Date of cancer diagnosis

Record the date of cancer diagnosis.

F.1.b Did the patient undergo an invasive therapy after diagnosis of bladder cancer that was not captured in Section D?

Record YES if invasive therapy was performed after the bladder diagnosis and is not captured in section D.

If NO or Unknown, SKIP to Section G, if applicable.

If YES, CONTINUE.

F.1.b.i Specify the invasive therapy:

Record an 'X' in the box that corresponds to the type of invasive therapy performed.

F.1.b Date of crossover to invasive therapy

Record the date invasive therapy was performed.

Section G - MORTALITY STATUS

G.1 Has the patient died since the last completed follow-up visit?

Record YES if the patient died since his last completed visit.

If YES, CONTINUE.

If NO or Unknown, SKIP to Section H.

G.1.a Date of death

Record the date of death.

G.1.b Probable cause of death

Record the probable cause of death.

Section H - CONCLUSION OF REPORT

H.1 Additional Comments:

If there are any additional comments, record them here.

INSTRUCTIONS FOR COMPLETING FORM T01 - PATIENT TRACKING INFORMATION

This form is completed during the baseline period, preferably at Screening Visit 1. This form is for the clinic coordinator's use only. It will never be entered in the computer or sent to the BCC.

This form is confidential and will only be used in case of emergency or if the patient is unreachable. Information captured on this form should be obtained and updated at each visit. Please keep in mind that all patients will need to be contacted at the end of the study. Therefore obtaining as much information as possible and keeping it updated is essential.

Section A - REPORT IDENTIFICATION

A.1 - A.3 See *Instructions for completing Patient Identification* on page 1 of this chapter.

A.4 Patient's social security number

Record the patient's social security number.

A.5 Patient's name

Record the patient's name.

A.6 Patient's address

Record the patient's current address.

A.7 Patient's home telephone number

Record the patient's home telephone number.

A.8 Name this telephone number is listed under

Record the name the patient's home telephone number is listed under in the telephone directory.

A.9 Patient's electronic email address if applicable.

Record the patient's email address if he has one.

A.10 Does the patient work?

If the patient has any job outside of the house should be recorded here.

If question A.10 is answered YES, continue. If question A.10 is answered NO, SKIP to Section B.

A.10.a Patient's place of work and address

Record the name and address of the patient's employer.

A.10.b Patient's work telephone number

Record the patient's telephone number at work.

A.10.c Name of immediate supervisor

Record the name of the patient's immediate supervisor at work.

A.10.d Supervisor's telephone number

Record the telephone number of the patient's supervisor at work if different from the patient's work telephone number.

Section B - EMERGENCY CONTACT

B.1 Does the patient have any relatives or friends that can be contacted in case of emergency?

Record YES if there is any relatives or friends that can be contacted.

If question B.1 is answered YES, continue. If question B.1 is answered NO, then skip to Section C.

B.2.a Person's name

Record the name of the relative or friend for contact.

B.2.b Relationship to the patient

Record the contact's relationship to the patient.

B.2.c Person's address

Record the contact's home address.

B.2.d Person's home telephone number

Record the contact's home telephone number.

B.2.e Name this telephone number is listed under

Record the name the contact's telephone number is listed under in the telephone directory.

B.2.f Person's work telephone number

Record the contact's work telephone number.

B.3.a Person's name

Record the name of the relative or friend for contact. This information is for an additional person to contact in case of an emergency.

B.3.b Relationship to the patient

Record the relationship the contact has to the patient.

B.3.c Person's address

Record the contact's home address.

B.3.d Person's home telephone number

Record the contact's home telephone number.

B.3.e Name this telephone number is listed under

Record the name the contact's telephone number is listed under in the telephone directory.

B.3.f Person's work telephone number

Record the contact's work telephone number.

Section C - ADDITIONAL NOTES

Record any additional notes that may be helpful in locating the patient in the future.

INSTRUCTIONS FOR COMPLETING FORM T02 - RECRUITMENT SOURCE TRACKING INFORMATION

This form is to be completed at Screening Visit 1 for all full-scale trial patients in order to track recruitment sources.

Section A - IDENTIFICATION

See *Instructions for completing Patient Identification* on page 1 of this chapter.

Section B - VISIT INFORMATION

B.1 Date of Screening Visit 1

Record the date of the first screening visit. This date must be the same date as the date in Question B.1 on Form B02 (Screening Visit 1 Inventory).

B.2 How did the patient find out about the study?

Record an 'X' in the box that corresponds to how the patient found out about the study.

Examples of each choice are listed below:

Community Event / Presentation

- ! Attended posters or booths, screenings via Health Fairs, PSA screenings, Prostate Cancer Awareness Week, or received handouts at a community event
- ! Presentations to social groups (e.g., AARP, men's clubs, churches, etc.)

Physician, Clinic, or Medical Records

- ! Physician, nurse, or any other health care worker referral
- ! Review of medical records, urology chart

Newspaper

- ! Paid advertisement, free advertisement or announcement
- ! News article
- ! Public Service Announcement

Television

- ! Paid advertisement, free advertisement or announcement
- ! News program
- ! Interview / Talk show
- ! Public Service Announcement

Radio

- ! Paid advertisement, free advertisement or announcement

- ! News program
- ! Interview / Talk show
- ! Public Service Announcement

Poster or Display

- ! Unattended posters or flyers - with or without attached cards to return or "tear off" telephone contact information
- ! Unattended distribution of pamphlets or brochures via poster or display

Mailing

- ! Letters mailed to patient
- ! Pamphlets or brochures mailed to patient
- ! Payroll inserts mailed to patient

Newsletter

- ! Society or Association newsletters (e.g., Fraternal Order of Police, AARP, Health Care Organizations, Universities, etc.)

Word-of-mouth

- ! Relative, friend, co-worker, neighbor, or acquaintance
- ! This does NOT include a "word-of-mouth" referral by a health care worker

Other

- ! Web site advertising, "surfing" the Internet
- ! Clinics "cold calling" patients
- ! Anything that cannot be categorized under 1-9
- ! Any answer here should be documented in the source records

B.3 Did the patient contact the national 800 number?

Record YES if the patient contacted the national 800 number.

INSTRUCTIONS FOR COMPLETING FORM T03 - PATIENT RELOCATION TRACKING INFORMATION

This form is to be completed any time a patient relocates and will be followed at another clinic. This form should be completed by the clinic from which the patient is moving (Current Clinic). Please fax this form to the BCC for data entry as soon as it is completed.

Section A - Patient Identification

This section is to be completed by the Current Clinic staff.

A.1 Current clinic number

Record the clinic number from which the patient is moving.

A.2 - A.5 See *Instructions for completing Patient Identification* on page 1 of this chapter. Record both the screening number and the patient number.

A.6 Date of last visit at the current clinic

Record the date of the patient's last visit at the current clinic.

A.7 New clinic number

Record the number of the clinic to which the patient is relocating.

A.8 Complete the following checklist

Record an 'X' in the appropriate box upon completion of each designated task. The tasks that should be completed are: notify the coordinator at the New Clinic, copy all CRFs and information in the patient binder, copy all source documentation, send copies to the New Clinic, and send any undispensed medication to the New Clinic.

Section B - Administrative Information

This section is to be completed by the BCC staff.

CHAPTER 12: DISTRIBUTED DATA ENTRY SYSTEM

MICROCOMPUTER SET-UP

The following instructions explain how to unpack and set-up the microcomputer.

1. **Unpack the computer system and monitor**
Save the boxes and packing materials for future use.
2. **Connect the keyboard, mouse and monitor**
Plug the keyboard cable and the mouse cable into the labeled round green and purple connectors on the back of the computer. Plug the blue end of the monitor cable into the 15 pin video connector and tighten the thumb screws on the cable connectors.
3. **Connect the parallel cable to the computer**
Connect the end of the parallel cable to the computer. Make sure the longest edge of the cable's connector is aligned with the longest end of the computer's parallel connector.
4. **Unpack the printer**
Remove the printer from the box and remove packing material from the printer. Save the box and packing material for future use.
5. **Attach the power cord**
Connect the power cord.
6. **Attach the parallel cable to the printer**
Attach the end of the parallel cable to the printer's parallel connector.
7. **Load paper into the printer's paper cassette**
Load up to 100 sheets of paper into the printer.
8. **Attach the modem cable to the computer**
Attach the 9-pin end of the modem cable to the *serial port 2* connector on the computer. Tighten the thumb screws.
9. **Unpack the modem**
Unpack the modem from the box. Save the box and packing material for future use.
10. **Attach the modem to the computer**
Plug the 25 pin end of the modem cable into the connector on the modem and tighten the screws.
11. **Attach the phone line to the modem and surge protector**
Plug the telephone line from the phone jack into the "IN" on the surge protector. Plug another phone cable from the "OUT" on the surge protector to the last connector on the modem (the leftmost one if looking at the back of the modem).
12. **Attach the power supply to the modem**
Plug the cable attached to the power supply that came with the modem into the modem's power supply

connector.

13. **Hook-up all equipment to power**

Plug the computer, monitor, printer and modem power cables into the surge protector. Make sure the power switch to the surge protector is set to *OFF*. Plug the surge protector into the wall.

14. **Turn on power to all components**

Turn on the surge protector. Push the round button on the front of the computer to turn it on. Push the rectangular button on the front of the monitor to turn it on. Push the power switch on the modem on. The printer has no power switch. If any equipment fails to operate, verify that the power cables are all securely connected at all ends.

Note: All power cables should be plugged into the surge protector. The surge protector should be plugged into the wall outlet. In addition, no other electrical machines should be plugged into the surge protector.

PASSWORDS

To comply with FDA guidelines for use of computerized systems in clinical trials, a sign-on procedure that includes a password has been implemented. When a form is requested for data entry or editing, the user must sign on with both valid initials and password. The software does not display the passwords on the screen as the user enters them. Special notes on passwords:

- ! Passwords must be 5-8 characters long, and are not case sensitive.
- ! Passwords expire after 6 months at which time the user is required to establish a new password.
- ! When a user establishes a password, it must be entered twice for verification purposes. Previous passwords cannot be used.
- ! Users may change their own passwords at any time by clicking on a new button that appears on the main data entry screen (a picture of a black key in a gray box).
- ! Users should choose a less than obvious password (avoid children's, spouses, and pet names), and keep the password to themselves.
- ! Note that passwords are only necessary to access form data, not for running reports.
- ! The initials of the keyer accessing the system appear in the bottom right hand corner of all data entry screens.

COMMUNICATIONS

The main use for the MTOPS Data Management PC is for study data entry and management. The Clinic PCS have been 'set up' for optimal use of time and resources for entering study data and transferring data to the computers at the BCC. To ensure accurate and timely transmission of data, as well as provide an efficient method for updating data management software, the system includes several features and standards that must be maintained.

BCC Access to Clinic PC

1. The BCC must have access to the Clinic PC at all times. Therefore, **the PC and modem must be turned on at all times** (even at night and on weekends and holidays). It is okay to turn the monitor off as desired, but this is not necessary.
2. The telephone linkage between the Clinic PC and the BCC must be operational at all times. When the PC is turned on or is rebooted and starts Windows, a communications program is run. This program (PCAnywhere) runs at all times and allows communication between PCS any time, even while Clinic personnel are using the

PC.

3. In order for the communications link to function properly, the modem must always be turned on before or simultaneously with the PC. **The AA light on the modem must be on at all times that there is no communication taking place** (whenever the BCC is not connected to the Clinic's PC).
4. If the modem 'drops' the Auto Answer (AA) setting, we may need to call the clinic via voice line to ask for the PC to be rebooted. Therefore, **if the AA light is not on, reboot the PC.**
5. When the BCC connects to a Clinic PC, BCC staff will usually try to initiate a process that takes control of the PC while no one is using it. If clinic staff are using the PC, a brief interruption may be noticed and any processes being performed will be slower. There will be a short interruption upon disconnection.
6. Many connection problems can be resolved by turning the computer off and on again. This can be done by the switch on the surge protector, so the surge protector should be easily accessible.
7. At times, it may be necessary for Clinic personnel to use the PC or look at the monitor while talking to us about a problem. A voice phone should be placed within reach of the PC.

Rebooting the Computer

It may be necessary at times to 'restart' the Clinic PC. 'Restarting' is required whenever the AA light is not on or as requested by the BCC. To reboot the computer, the following steps should be executed.

1. Click the "Start" button on the bottom left side of the screen.
2. Select "Shut down".
3. Select "Restart" and click "OK".
4. Please note that 'restarting' should not be performed while a data entry form is on the screen (unless the system is 'locked'), as it could result in the loss of data.

Resetting PCAnywhere

PCAnywhere enables the BCC staff to call clinic computers to retrieve data, update software, and troubleshoot as needed. *PCAnywhere* should be in "wait mode". If BCC staff is unable to connect to the clinic computer, they will contact clinic staff to verify PCAnywhere is in "wait mode" and may request clinic staff to "reset" PCAnywhere. To reset PCAnywhere, the following steps should be executed:

1. Find the *Symantec PCAnywhere* icon on the left side of the screen and double click on it to start it.
2. The clinic name will appear. If it is not bolded, click once on it to select it.
3. There is a tool bar directly above the name of the clinic. The left most icon in the tool bar is a small computer with a lightening bolt going into it. Click on that to launch host, which will reset *PCAnywhere*.

Data Extraction and Transmission

The study data is transmitted to the BCC weekly. The weekly process occurs in two steps. First the data is extracted from the databases, then it is transmitted to the BCC. The following points detail information regarding data extraction and transmission.

- ! The transmission process begins with the extracting of new transactions from the data bases on a weekly basis. It is currently scheduled for 1:00 A.M. on Tuesday mornings.
- ! For the extract to be successful, **the Event Manager must always be running**. The Event Manager is shown as an icon in the lower left corner of the Windows screen. If it is ever noticed that the event manager icon is missing, Windows must be exited and restarted.
- ! After the transaction extract is complete, BCC staff will call the Clinic PC to transfer the extracted data. This will usually occur between 7:00 A.M. and 11:00 A.M. Eastern Time Tuesday mornings and takes a few minutes. **All clinic personnel that use the PC should be aware of this schedule**. During the transmission process, nothing else should be performed on the PC because this will slow down the transfer process and increases the possibility of communication failure. If the transmission does not complete properly, data files may be left on the clinic PC, possibly causing future extraction and transmission problems. When a data base is accessed, there will be a notification as to this condition. The notification should be printed and sent to the BCC.

Communicating with the BCC via the 'Chat' Feature

When BCC staff calls the clinic PC for any reason, they may want to talk to a person via the 'Chat' option. This option can be initiated by either the BCC or by the user at the clinic. To initiate the 'Chat' option, select 'Chat' from the online menu. Then, type in the box that appears on the screen, hit the Enter key to send the message and wait for a response. Please note that the Enter key must be hit to send the message to the BCC Staff. To end 'Chat Mode', close the chat box.

Please note that the 'Chat' option is the only selection that should be made from the online menu. Changing or selecting other options may cause damage to the clinic PC setup that cannot be corrected remotely. It is imperative that the 'End Session' is never selected. Only BCC personnel should adjust options or end sessions.

WINDOWS FEATURES

The following features are available within the Windows system and are the most commonly used for MTOPS purposes. Most of them will be visible when the Windows session screen is visible.

The following features appear in the Quick Access Group:

MTOPS Software Icon is used to initiate the MTOPS Windows Menu.

Symantec PCAnywhere Icon is used to start up the communication software. This should not be used unless instructed by the BCC staff.

The following features appear in the MTOPS System Group:

MTOPS Data Entry Icon is used to initiate the MTOPS data entry system menu.

MTOPS Reports Icon is used to initiate the MTOPS reports selection menu.

All files on drive C Icon is used to initiate a backup. Since tape backups are handled automatically by the clinic computer every Tuesday and Friday night, this icon is here in case clinic staff want to make an extra backup.

MTOPS Theme Audits Icon is used to initiate the MTOPS theme audit selection menu.

Status Database Data Entry Icon is used to initiate the MTOPS status database entry and editing software.

Print Status Database Icon is used to print the status database and reports (Active Patients Report, Inactive Patients Report, Discrepancy Report, and a Summary Report).

Elapsed Days Icon is used to access a calculator for elapsed days from one visit to the next visit.

Clinic Staff Database Icon is used to initiate the MTOPS clinic staff database.

PAC Reports Icon is used to initiate the PAC reports selection menu.

The following features appear across the bottom of the Windows screen:

McAfee Vshield and **McAfee Shield Scan Scheduler** are used to keep the computer virus-free.

Task Scheduler

Backup Exec Scheduler is used to run Tuesday and Friday backups.

PCAnywhere shows the status of the remote access system. It must be visible when the Windows session screen is visible. If this icon is not in "Wait mode", reset PCAnywhere (see Resetting PCAnywhere).

Event Manager is used to schedule other scheduled events such as the weekly data extraction and automatic status database printing.

DATA BACKUPS

Introduction

There are two hardware mediums available for making backups: the 3 1/2" diskette drive and the tape drive. The tape drive is normally used for backups due to the convenience of tapes and the great number of diskettes that would be needed. However, if the tape drive becomes defective and it is necessary to make a backup before it can be repaired, diskettes can be used.

When To Do A Backup

The backups are run automatically Tuesday and Friday evenings at 11pm EST. If clinic staff want to do an extra backup, run 'All files on Drive C backup' located in the MTOPS system group.

Using Tapes

Two tapes will be used to backup the data. The tapes are labeled 'Tuesday backup' and 'Friday backup'. A tape should be in the clinic machine at all times and kept in the unlocked position. Monday morning remove the 'Friday backup' tape and insert the 'Tuesday backup' tape. Wednesday morning remove the 'Tuesday backup' tape and insert the 'Friday backup' tape.

MTOPS DATA ENTRY - MAIN MENU WINDOW

Use the mouse to click on the MTOPS Data Entry icon to show the Main Menu Window. All processes for entering,

modifying, and browsing the database are initiated from this window. Each process can be accessed from the menu bar (the strip at the top of the screen containing "File" "Options", etc.) while a few processes can also be invoked directly from the tool bar (the icons just below the menu bar).

File Menu

Allows the following processes:

4. Data Entry and Editing
5. Adding All Forms for a Visit (by patient)
6. Exiting the Data Entry System.

Data Entry / Editing

Both the **Data Entry/Editing** selection under the **File** menu and the folder button provide access to all MTOPS forms.

Upon selecting **Data Entry/Editing**, a window of file folders is shown. Each type of form (B forms, E forms, etc.) is located in one of the folders. Click on the folder desired and the list of available forms will be displayed.

Once a form is selected, a mode of entry must be selected, add or update (update is the default). Two buttons are shown at the bottom of the file folder: **Add** and **Update**.

Add: To add a new form, click on the **Add** button prior to clicking on a form button. After each record is entered and edited, it is added to the database. Then a blank form is automatically displayed for entry of another form. The browse table and previously entered records are not accessible in the add mode.

Update: This mode allows browsing, changing and deleting, as well as adding records. Update mode is the default selection, so the **Update** button is already selected.

Once a mode and form are selected, click on the button for the desired form and a new window will open.

Add All Forms for a Visit

The **Add All Forms for a Visit** selection under the **File** menu permits entering of all of the forms pertaining to a particular visit for one study participant. After selecting **Add All Forms for a Visit**, another menu listing the available visits is presented. Click on the visit desired and a new window is displayed that shows all forms required for the visit and any optional forms available. Click in the check box for each desired optional form. Then, click on the **OK** button to begin the data entry process for the visit or **Cancel** to terminate the selection.

For this method of adding data, each form is presented in alpha-numeric order, ready for data entry for one study participant. After the first form is entered and edited, the first page of the next form is presented with the key information already entered. Each subsequent form will be pre-stamped with the key information in the same way. When the last form is entered for the selected visit, the system will return to the main menu window.

Options Menu

Allows access to the following utilities and testing processes:

1. Repairing database file indices
2. Changing patient initials and date of birth on all forms
3. Clearing the test database for certification exercises
4. Extracting new test data

Repair Indices

Index files keep track of the records and their order in the databases. The indices are maintained as forms are added, changed and deleted. It is possible that, in the event of a power outage, invalid program termination or other

unintended system interruption, that the indices could become corrupted. The **Repair Indices** option should be used if a data entry/edit process is terminated abnormally or if added records do not appear on the browse list. There is no user interaction during this process. Simply double-click the menu item and wait for the process to complete.

Change Inits/DOB

After the B02 Form has been entered, subsequent forms will extract the patients initials and date of birth from the B02 so that the person entering data does not have to enter them again. It is necessary to review these items on the computer screen to verify that they are the same as those written on each CRF. It may be necessary to correct these items at a later time. To do so, initiate the **Change Inits/DOB** menu item and enter the patient's Screening Number and appropriate new ID values. This feature will change these values on all forms for that patient.

Clear Test Databases

This option is used to empty all records from the Test Database which is used for practice and certification exercises. This feature should be used prior to using the Test Database for the first time and any time a new keyer needs to be certified. When this option is selected, a confirmation message will appear to verify that the user wants to delete all records.

Extract New Test Data

This option will select all 'new' data entered into the Test Database and copy it to files that can be downloaded to the BCC computer. It extracts only that data from the Test Database that was entered since the last extraction, or since the last 'Clear Test Databases' action. Subsequent extractions will include only that data entered since the last extraction and will overwrite any previously extracted data. So, if data is extracted, no more data entered and then extracted again, the files to be sent to the BCC will be empty. If data is extracted and sent to the BCC, and more data added or some forms changed, followed by another extraction, only the changed records will be included in the extraction files and sent to the BCC.

Help Menu

The **Help** menu item provides an 'About...' feature that, when selected, will present a box that displays the name and version of the software and the address and Fax phone number for the BCC.

Buttons on the Main Window

There are thirteen buttons at the top of the main screen. These buttons provide easy access to some of the features listed in the file, options and help described above, as well as to some of the other features of the MTOPS software.

- ! The grey folder - file folder of MTOPS forms
- ! Repair indices - repair indices
- ! Inits/DOB - change inits/DOB
- ! Extract test - extract new test data
- ! MTOPS reports - main reports menu
- ! Theme audits - main theme audits menu
- ! Update status - status database for all patients
- ! Print status - prints the current status database for all patients
- ! Elapsed days - calculates number of elapsed days between two dates
- ! Clinic staff - Clinic Staff Database menu
- ! PAC reports - PAC reports menu
- ! Red door - exits the data entry software

Select Production/Test (at bottom of screen)

This option allows for the selection of either the Production Database or the Test Database.

The **Production Database** is used to store all actual study forms. Everything being added for actual patients should utilize this Database. The **Test Database** is used for practicing and certification exercises. It is utilized by new keyers to learn how to use the system and to enter BCC supplied forms to gain certification for using the system.

The Test Database option must be selected prior to entering any test forms. Test data should never be entered into the Production Database as that data would be uploaded to the BCC mainframe computer and become part of the Master Database used for analysis.

The Production Database is automatically selected whenever the MTOPS Data Entry System is initiated. It is not necessary to start the program and select Production Data, even if Test data was being used at the end of the last session. But, it is necessary to select Production data if the Test Database was being used and Production data is to be accessed without ending the session. If in doubt about what Database is being accessed, invoke this option for verification.

Double Data Entry (at bottom of screen)

This option is used to select the mode of double data entry for adding new forms to the Test Database. Double data entry is always required for the entry of new records into the Production Database. Selecting this option and attempting to turn double data entry *off* while accessing the Production Database will have no effect. However, this is an option for the Test Database only and is used based on the requirements of practice and certification exercises. Click on the appropriate button to either turn double data entry on or off.

When double data entry is turned on, every record that is added must be entered again immediately upon completion of the final page. The 'key' fields are not entered again. Once a form is completed the first time, the first page of that form will be redisplayed with all fields blank except for the key fields. The cursor will be at the first data (non-key) field. The form should be reentered exactly as before, including the case and spelling of text fields. Any discrepancies between the two entries will result in an error message and will require reentry of each field in error, two more times.

Toggle for Trial Data / Pilot Data (at bottom of screen)

Click on the appropriate button to access either the full-scale trial data or the pilot data (for pilot clinical centers only).

MTOPS DATA ENTRY - CASE REPORT FORMS ENTRY SOFTWARE

Browse Table

This is a blue screen displayed upon selection of a specific CRF while in update mode. This table displays the key fields for all records in the selected database.

To move within the browse screen:

PgUp/PgDn or **Up/down cursor** keys view more records.

Left/right cursor keys view different key fields.

To move between the browse screen and the data entry screen:

Esc key switches to data entry form last added, browsed or edited.

F8 key or **Enter** key switches to data entry form for current highlighted record.

Data Entry Screen

An example of a data entry screen appears below. The contents and paging of the data entry form is not necessarily the same as the paper form.

```

File..  Mode..  eXit                               KEY
                                                B02.2
                                                PAGE 1

NIH - BPH TRIAL
SCREENING VISIT 1 INVENTORY

Part I / IDENTIFICATION

0. Patient Identification
  1. Clinic number           07
  2. Screening Number       30001
  3. Patient's initials     SWBH
  4. Patient's date of birth 09/29/40

11. Visit Information
  1. Date of visit          06/11/95

02. General Information
  1. Race                   1
  2. Marital status        1
  3. Grade level last completed 1

BROWSING VISIT 1 INVENTORY RECORD
  
```

The "File... Mode... eXit" buttons in the top left corner indicate availability of function menus; press **Alt+the capitalized letter** to invoke each one.

The "KEY/DATA" flag in the top right corner indicates that current highlighted field is either a key field or a data field.

The action message in the bottom left corner reminds the data entry person that the current record is being added, browsed, changed or deleted.

The clinic number is always pre-entered, it will appear on each form automatically.

File Menu

Press **Alt+F** to invoke the File Menu. Use **up/down cursor** keys and **Enter** key to select function, or press upper case letter in line describing desired function. Alternatively, press associated function key (without using Alt+F).

Menu Option	Function Key	Function
Browse	F8	Display the blue Browse Table with current record as highlighted record.
Labels	F6	Invoke a function that allows printing of address style labels, if available for current form.
Report	F5	Invoke a function that allows printing of a predefined report, if available for this form.

Repair index	---	Restructure index for current form; similar to repair indices on MTOPS data entry main menu.
Table/print	F9	Invoke a table listing of available values for certain fields, from which a choice can be made via the up/down cursor and Enter keys. Note: If a clinical term can not be found in the table, type in the response. A report will be printed after data entry which then can be subsequently sent to the BCC for review. If there is no table available for the highlighted field, F9 will print the current form on the clinic printer.
Undo changes	F7	Remove an added record or remove changes to an edited record before moving to another record.
eXit form	F10	End the data entry session for the current form and return to the form selection menu.

Mode Menu

Press **Alt+M** to invoke the Mode Menu. Use **up/down cursor** keys and **Enter** key to select function, or press upper case letter in line describing desired function. Alternatively, press associated function key (without using Alt+M).

Menu Option	Function Key	Function
Add record(s)	F2	When in update mode, invoke add mode to enter new records with automatic saving and screen clearing after each record is complete.
Change key	---	Modify any of the fields that comprise the key identifiers as indicated by the "KEY" flag in the upper right corner of the data entry screen.
Delete record	---	Remove a record that has already been saved to the data base.
Find key	F3	Searches for the record with the closest matching key to that entered on the screen.
New record	F4	End entry or modification of a record, invoke editing and, if no errors exist, clear the screen so that a new record can be entered.
Paste field	F11	Copy the value entered on the previous record for the same field. This function is only available when entering more than one of the same form.

Data Entry Hints

Use **Up Cursor** key to move to the previous field.

Use **Down Cursor** or **Enter** key to advance to the next field, and the next page at the end of a page.

Use **PgUp/PgDn** keys to move backward and forward through pages of a form.

Use **Ctrl+Down Cursor/Ctrl+Up Cursor** to move backward and forward from form to form in the order they are listed in the blue Browse screen.

Saving Entered Case Report Forms

When entering new forms in Add Mode, the record is saved when the verification process is completed. When entering new forms in Update Mode, the record is saved when the form is completely entered. When editing forms in Update Mode, the new information is saved when the field is exited.

Deleting a Case Report Form

To delete a Case Report Form that has been previously entered, press Alt + M to invoke to the Mode Menu and select "Delete record". This will remove the record from the database.

Exiting a Case Report Form

Press F10 to exit and end the data entry session for the current form. This will save all information entered. If it is necessary to exit a form without saving new information entered, press the F7 key to undo the changes. If in update mode, to exit to the blue Browse table, press F8.

Updating Values in the Different Types of Fields

In order to update a value already entered, the record must be accessed in the Update Mode. To change a "DATA" field, simply enter the new value. The only way to change a "KEY" field is to invoke the "Change Key" option in the Mode Menu. Once the value has been changed, move the cursor down until a DATA field is reached (indicated at the upper right of the screen).

Error Box

The Error box appears whenever an illegal value is entered. There are two types of error box. If the box appears as a one line box indicating an error, the field must be corrected, changes must be removed (Undo-F7) or the entire record must be deleted. When the box includes choices that explain the nature of the error, either the field can be corrected or a reason for the error can be selected. The error code assigned to a field becomes attached to that field until it is corrected. It will appear in the upper right corner, indicated by EC (error code). Use the F12 key to invoke the error code selection box for a field that is currently highlighted. If an error code is assigned to a field for which there was no edit, that error code will not automatically be cleared when a value is entered or changed in that field.

Error Handling

Edit criteria may require that a value be entered into a field and/or that the value entered be within a certain range. Edit criteria may be as simple as requiring that a field not be left blank, or as complex as to require that certain values be entered based on other fields on the same form.

When a field is entered incorrectly, the data entry person will be notified of the error in one of two ways:

1. The display of a single line error message. The message displayed may begin as "INVALID ENTRY..." or may more specifically describe the error. This type of error notification indicates an error that is required to be corrected. There is no provision for bypassing this error, and, if the error was not a typographical error, then the form or changes to the form must be removed (F7 Undo).
2. An error message such as "INVALID ENTRY..." while also displaying a box of possible reasons for entering the field in violation of the edit criteria, which follows:

INVALID ENTRY - REENTER VALUE OR UNDO CHANGES

Return to field without setting error code

? symbol coded on form; known temporarily missing or invalid response

@ symbol coded on form; known permanently missing or invalid response

1) Keying problem - response is missing with no explanation for error

2) Keying problem - response keyed as coded; no explanation for error

3) Keying problem - response cannot be read, so field is left blank

4) Keying problem - more than one response, so field is left blank

Select reason for error or press Esc to reenter value

By selecting one of the reasons, the error condition can be overridden. Overriding the error allows the invalid data to remain in the data base, but the selected reason code will be "attached" to it and serve as an explanation for the error. Some errors may remain in the data base (@) while others may be corrected in the future (? 1 2 3 4).

To select a reason, move the highlight bar with the cursor control keys to the desired reason and press Enter. The first character on the line chosen becomes the error code associated with the invalid field. If the data entry person would like another opportunity to enter a correct value, they should press Enter while the first option is highlighted ("Return to field..."), or press Escape. No error code will be attached to the field. All fields for which the error box appears must either be entered correctly or assigned an error code.

Any field with overridable edit criteria will automatically display the error code box when an invalid entry is made or if it is left blank when an empty value is not allowed. Sometimes the data entry person may not be able to enter a value in the field (e.g. if the value written on the form is unreadable or too many selections for a multiple choice question were checked). In this type of situation, the data entry person can leave the field empty and press the F12 key. This will cause the error code box to appear and a reason for not entering the response as written can be selected.

Once a reason code has been attached to an error, the error explanation box will no longer automatically appear whenever the field is highlighted. Whenever a field with a value in error is highlighted, the error code associated with it appears in the upper right corner of the screen (see below). This allows for easy browsing of the error codes attached to a form.

If a field in error is changed and the new value is still in error, then the explanation box will reappear with the prior reason code already highlighted. The same, or a new reason, can then be selected.

If a field in error (codes 1, 2, 3, and 4 only) is changed to a value that is no longer in error, the error code will automatically be removed and there is no need for the data entry person to perform any action. (It is not necessary to press the F12 key to attempt to remove the error explanation code for a "repaired" field.) If it is desirable to change an error explanation, simply highlight the desired value, press the F12 key and select a new reason for the current error condition.

File..	Mode..	eXit	EC 1	DATA
THE EFFECTS OF MATERNAL LIFESTYLES ON INFANT OUTCOMES				NC03.1
MATERNAL HOSPITAL INTERVIEW - ACCEPTED STUDY				PAGE 2
5/10017				
3.	Did you see a doctor or nurse for Prenatal care?		2	Error Code
a.	If yes, how many visits did you have?		0	
b.	When did you go for your first prenatal care visit?		/ /	
4.	Have you been hospitalized during this pregnancy?		✓	Highlighted Field
5.	What was the date of your last menstrual period? (LMP)		/ /	
6.	What was the date the doctor estimated birth? [EDC]		05/15/93	
7.	What was your weight before this pregnancy?		135 lbs	
8.	What is your height?		5 ft 6 in	
9.	Were you on any special diet during this pregnancy?		.	

Guidelines for Choosing an Error Code

There are several guidelines for choosing an error code from the error explanation box.

- ! The "?" and "@" error codes may only be used if a question mark or an ampersand is written on the case report form.
- ! Error Code 1 is only used when the information is missing and there is no "?" or "@". No values are ever keyed along with an EC1.
- ! Error Code 2 is only used when the computer will not accept the value written on the case report form (e.g. either it is to of range or an invalid date). A value can be entered along with an EC2. Only use the EC2 if the "invalid entry" error box appears.
- ! Error Code 3 is selected when the data on a case report form cannot be read (e.g., the "X" falls across two boxes, the value has a decimal point when there is no decimal point on the case report form, the handwriting is unclear). The field will always be left blank when keying an EC3.
- ! Error Code 4 is selected when there are clearly two or more answers (two distinct "X's" or two distinct circles) to a question that requires only one answer. The field should always be left blank when keying an EC4.

Special Instructions for Error Handling

The important points to remember in handling error conditions are as follows:

- ! Some error conditions cannot be overridden (an error code chosen to explain). Variables that must be entered correctly display a one-line message when an error condition exists. These errors must be corrected or the forms must be exited and reentered when corrected.
- ! An error explanation box will automatically appear when erroneous data is entered in a field that allows an error code (overridable).
- ! If a value cannot be entered because it is missing, illegible, etc., and the error explanation box does not automatically appear, press the F12 key to pop-up the error explanation box. For error codes chosen in this manner, the error code is not removed automatically when the data is corrected. Once the data is obtained, the error code must be manually removed. Press the F12 key and select the option "Return to field without setting

error code”.

- ! "Explained" errors will not re-display automatically but the attached error code will display in the upper right corner of on the screen.
- ! To display or change an error explanation, press the F12 key for the desired field. In order to remove an error code, press Enter (Return to field without setting error code).

Mock Randomization

Mock randomization is a feature that allows clinic staff to check a screening patient's eligibility status at any time prior to randomization, thereby eliminating the need for randomization exceptions. The mock randomization feature can be accessed under the "B" file folder in the Windows software. All of the eligibility criteria are checked and any criteria which are not met will be listed on the screen, with an option to print the information.

A mock randomization can be performed anytime after Form B02 (Screening Visit 1 Inventory) has been entered and as often as is necessary. The mock randomization feature only checks a patient's eligibility status --- no data is altered when performing a mock randomization. Additionally, performing a mock randomization does not actually randomize a patient.

Randomization Procedure

To randomize a patient, all necessary forms must be entered in the computer (see Checklist for Preparing for Randomization, in Chapter 3, page 9). Form B04 (Randomization Information) must be entered last. There are two ways in which to enter Form B04 and randomize.

1) Select Add Mode.

1. Enter Form B04 in the Add Mode.
2. Note that the cursor will skip section G on page 3 during the first and second phase of double data entry.
3. Exit the Add Mode.
4. Select the Update Mode.
5. Access the appropriate Form B04.
6. Go to section G and attempt to randomize by typing an 'X' on Question G.

OR

2) Select Update Mode.

1. Enter Form B04 in Update Mode.
2. Note that the cursor will skip section G on page 3 during the first and second phase of double data entry.
3. After the form has been entered, the system will put the cursor back at the beginning of the form just entered.
4. Go to section G and attempt to randomize by typing an 'X' on Question G.

PROBLEM/REQUEST LOG

The Problem/Request Log form (See Appendix) is used to report all situations encountered with the data entry and reporting study software which warrant BCC attention.

This form should be used for questions, concerns or requests concerning edit requirements, abnormal program terminations, anything perceived as an error or problem and desired changes and new features or reports.

Complete the entire form and fax it to the BCC as soon as possible. No cover sheet is necessary. Please note that all information on the top of the form must be completed (to, from, date, center number and center name). Check whether the form concerns a problem with an existing feature, or a request to change or add a feature, form or report. Enter the form or report number and include a description using as much detail as possible to accurately document the problem or request. If a program displays a message box as shown on the log, copy the contents of that box to the log.

Note: This form must be faxed and no follow-up telephone call is necessary. This is the most efficient way of communicating with the software personnel at the BCC.

The BCC staff will fax the form back the clinic (and possibly to other clinics if a problem or request may also apply to them) with a description of our actions so that the clinic staff will know when the problem or request has been handled.

FOLLOW-UP PSA AND AUA REPORTS

Reporting follow-up PSA and Free PSA results to the clinics is an automated system. These reports are processed and results faxed after transmission of data every Tuesday. Included in the automatic reporting are listings of discrepancies between Form R07 (PSA Collection Report) and the Diagnostic Center (Diagnostic Center) data. The data is matched by patient information and date. If both Diagnostic Center data and a Form R07 are entered, but they have different dates, both records will appear in the listings. These listing will keep the coordinator up-to-date on the status of the results. Results will not be reported until all discrepancies are resolved.

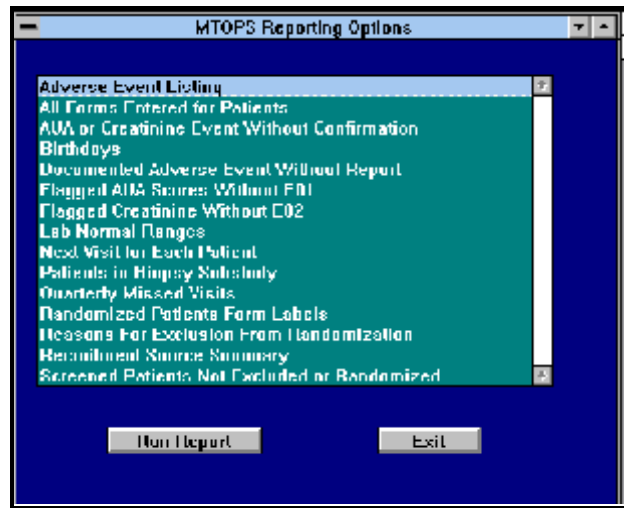
In addition to the PSA reports sent to the clinics on a weekly basis, a report of symptom scores entered during the past week that indicate a 4 point rise will also be sent. The report will indicate the patient number, the date of the AUA Symptom Questionnaire (Form Q01), the symptom score and the baseline symptom score. This report is used to help flag the rises to ensure that rises, confirmation visits, and hence primary endpoints are not missed.

REPORTS FOR THE MTOPS SYSTEM

Reports have been developed for the MTOPS system to be used on the clinic microcomputer. The reports can be accessed by choosing the **MTOPS REPORTS** icon which is located in the **MTOPS System** group or by the **MTOPS Reports** button located at the top of the data entry screen.

How to Select Reports

1. Position the mouse on the MTOPS Reports icon and click to activate reports. The following panel will appear with a menu of the MTOPS Reports:



2. Position the mouse cursor on the title of the desired report. Click anywhere on the report title to select it. Then click on 'Run Report'. A panel will appear with any selections available for the chosen report.
3. Select the report destination.
 - a. **Printer** will send the report to the laser printer.
 - b. **Screen** will show the report on the screen.
4. In addition to these choices, some reports have additional selections that the user may make:
 - a. **Screening number range** - all individuals with screening numbers within the range selected will be reported. If no range is selected, the default range of S0001 - S9999 (all patients) will be used.
 - b. **Date ranges** - all records with visit dates within the range selected will be reported. If no date range is selected, the default range of 01/01/93 - 12/31/02 (entire study) will be used.
 - c. **Patient number range** - all individuals with patient numbers within the range selected will be reported. If no range is selected, the default range of 1 - 999 (all patients) will be used.

Reports With No Data

If a report is chosen for which there is no data, a message will appear both on the screen and/or the printer. This eliminates confusion which could occur if a report is selected and no output is produced.

Description of Each Report

1. Adverse Event Listing

This report provides three optional methods for listing adverse events (Forms E04, E05, and E06). Three different Reports can be generated: all adverse events for a range of patients, serious adverse events, and continuing adverse events. This report can be run for a selected range of visit dates.

This report will be helpful for patient visit preparation. All continuing adverse events for a patient or a range of patients can be printed indicating which old adverse events need to be discussed at the upcoming patient visit. All serious adverse events can be printed to report to the local IRB. Additionally, it can help identify discrepancies between E05/E06 for a serious adverse event and identify continuing adverse events that should be resolved.

2. All Forms Entered for Patients

This report provides a complete inventory for all forms entered in the computer. The report lists the screening number, patient ID number, initials and all forms and visit dates entered for the chosen patients. For the Adverse Event Report (Form E04), the adverse event short description and onset date appear. The user may select a range of visit dates and screening or patient numbers on which to report. If no range is chosen, the default of all patients will be used (S0001 - S9999). The report will be printed by patient, CRF and visit date.

This report can be helpful in verifying that all forms are entered (with correct dates) before randomizing a patient or when responding to theme audits.

3. AUA or Creatinine Event without Confirming Visit

This report provides a list of patients for whom an AUA Symptom Score Event (Form E01) or Creatinine Rise Event Report (Form E02) was started, but the confirming visit section was not completed or was explained as permanently missing. The report lists the patient number, the date of the initial visit from Form E01 or Form E02, and the deadline for the confirming visit. The report will be printed in deadline date order.

This report can be helpful in verifying that an AUA symptom score rise event or a creatinine rise event is not missed. Consequently, this report should be run quite often.

4. Birthdays

This report lists all randomized patients with birthdays falling within the specified date range. The report will be printed in birth date order.

This report can be helpful in sending birthday cards to patients.

5. BCC Mailing Labels

This report prints mailing labels for the Biostatistical Coordinating Center.

6. Compliance - Dose of Doxazosin

For randomized participants who have completed one or more quarterly follow-up visits, this report lists the following information from the most recently quarterly visit; the number and percentage of participants reporting the following: no doxazosin use since the last visit, use of the 1mg dose of doxazosin, use of the 2 mg dose of doxazosin, use of the 4 mg dose of doxazosin, use of the 8mg dose of doxazosin, and use of doxazosin, but no dose indicated.

This report can be helpful in tracking coded doxazosin usage.

7. Compliance - Over Time

This report lists total compliance $\geq 80\%$ and total adjusted compliance $\geq 80\%$ for three-month periods beginning 01/01/96. The number and percentage of participants reporting $\geq 80\%$ compliance and adjusted compliance to

doxazosin and finasteride is reported. Please note that adjusted compliance refers to compliance in participants who are currently taking the coded medication.

This report can be helpful in tracking clinic doxazosin and finasteride compliance over time.

8. Compliance - % \geq 80% Compliant @ Quarterly Visits (GRAPH)

This report graphically displays information about the percent of patients who have \geq 80% adjusted compliance to the coded medications at quarterly visits. The values displayed graphically here are available in the "Total Adjusted Compliance \geq 80%" column of the "Compliance - Over Time" report.

9. Compliance - % \geq 80% Compliant @ Quarterly Visits

This report lists total compliance and total adjusted compliance to coded medications for all quarterly visits and for the most recent quarterly visit. For each of these categories, the number of quarterly visits and the percent of those visits with compliance \geq 80% to coded doxazosin and finasteride is listed. Adjusted compliance excludes participants who have not taken coded doxazosin or finasteride since the last visit, and is therefore compliance among current coded doxazosin and finasteride users.

This report can be helpful in monitoring clinic doxazosin and finasteride compliance data.

10. Data Entry Delay

This report generates information about the lag time between collecting data and entering it into the computer for selected forms (B02, B03, B04, F01, F02, P01, Q01, Q02, Q03 and R07). The default time period is the last six months but the report can be run for any time period up to 6 months long. The reports lists the number of each CRF entered, median delay, 25th percentile and the 75th percentile.

11. Dissatisfied with Quality of Life

This report lists all patients that have been dissatisfied with their quality of life as reported in question C.1 on the AUA Questionnaire (Form Q01). The report can be printed for each patient for the past year or on the most recent Q01 visit. The report lists patient number, initials, target date of next visit, date of Q01 reporting dissatisfaction and the answer recorded for quality of life (question C.1).

12. Documented Adverse Event Without Report

This report provides a list of all patients who have experienced some type of adverse event according to the Standard Follow-Up Visit Inventory (Form F01), the Missed Follow-Up Visit Report (Form F04), or the Titration Visit Inventory (Form F06), and are missing an accompanying Adverse Event Report (Form E04 or E05). The report lists the patient number, initials, date of visit, and the form on which the adverse event was indicated. The report will be printed in date order.

This report can be helpful in ensuring that an adverse event is documented promptly. Consequently, it should be run every week.

13. Flagged AUA Scores Without E01

This report provides a list of all patients with an AUA symptom score of 4 (or 8 for pilot study patients) or more points greater than baseline who are missing an accompanying AUA Symptom Score Event Report (Form E01). The report lists patient number, initials, baseline AUA symptom score, elevated AUA symptom score, the date of rise according to the AUA Symptom Questionnaire (Form Q01) and whether the patient has crossed over to invasive therapy. The report will be printed in date order.

This report can be helpful in ensuring that increases in the AUA Symptom Score are documented promptly.

14. **Flagged Creatinine Without E02**

This report provides a list of all patients with a creatinine rise recorded on a Major Follow-Up Visit Inventory (Form F02) who are missing an accompanying Creatinine Rise Event Report (Form E02). The report lists patient number, initials, creatinine at baseline, elevated creatinine according to Form F02, and the date of the rise. The report will be printed in date order.

This report can be helpful in ensuring that increases in creatinine levels are documented promptly.

15. **Lab Normal Ranges**

This report provides a complete list of all Clinic Laboratory Normal Range Report (Form R01) information for the clinic. These are listed in test order. If more than one laboratory is used at the clinic, the information for each laboratory will appear separately.

A few examples of how this report can be helpful are verifying that the data was entered correctly and comparing normal ranges to a laboratory report to check for changes in the ranges.

16. **Maximum Flow Rate Over Time (TABLE)**

This report lists all maximum flow rates, voided volumes and post void residuals for an individual patient at all screening and standard visits (B03 and F01). Patient number, screening number and initials appear at the top of each page, followed by date of visit, CRF number, maximum flow rate, voided volume and post void residual.

17. **Maximum Flow Rate Over Time (GRAPH)**

This report graphically displays information available in the “Maximum Flow Rate Over Time” report.

18. **Next Visit for Each Patient**

This report provides a list of patients and the target dates and window for their next visit. The user may run the report on a patient number range and/or a time range of last visit dates. For all patients, except those who have become inactive (and reviewed by the CRC) or died, the target for the next visit date is based on the last form entered. This report takes into consideration those patients on abbreviated protocol as reported in the status database.

The report lists the patient number, initials, the form completed at the last visit, the date of the last visit, the target date for the next visit, the window for the next visit, if the next visit is a six month or major visit, and if there are any adverse events still continuing. The report will be printed in patient order.

This report can be helpful in scheduling visits. It will also help to identify patients for which unresolved adverse events should be addressed.

19. **Not Seen >= 70 Days**

This report lists all active participants who have not been seen in 70 days or more. Patient number, initials, date of last visit and days since the last visit are listed. Information is displayed in order of the number of days since the last visit.

This report can be used to identify patients who have missed one quarterly visit, before they are due for their next visit.

20. **Patients in Biopsy Substudy**

This report provides a list of all randomized patients, including all pilot study patients, who are participating in the biopsy substudy. The report lists the patient number, initials, the date of randomization, the date of baseline biopsy, the date of the year-one biopsy, R06 date if year-one biopsy not done, target of EOS biopsy and date of EOS biopsy when completed. The report can be printed in patient or target of EOS biopsy order. Patients who have become inactive or died will be indicated as such. Additionally patients diagnosed with cancer on Form R08 will be indicated as only

needing a TRUS. **Note:** a biopsy is considered a year-one biopsy if it is performed within the window of 3 months prior to and 6 months post the target date of the one-year visit.

Additionally, an “audit listing” printed after the reports provides a list of missed year-one biopsies that do not have a corresponding Missed Biopsy Report (Form R06).

This report can be helpful in tracking the number of patients who are participating in the biopsy substudy in order to identify patients who are due for follow-up biopsies. Additionally, it can help identify patients who are missing Form R06.

21. Post-randomization Forms with Discrepant Visit Date/Week

This report lists all post-randomization visits for a patient that have a date and week that are discrepant by patient calendar. For each patient, the report lists patient number, screening number, initials, randomization date, form, visit date and visit week recorded.

This may be helpful in avoiding and/or addressing theme audits.

22. PSA, DRE and TRUS Volume

This report lists all PSA, DRE and TRUS volume information gathered from B02, B04, P01, F02 and the Diagnostic Center. Patient number, randomization date and initials appear at the top of each page, followed by information about each test: visit date, test, type, results and comments. The user can select a patient number range. Each patient’s information is displayed on a separate page.

23. Primary Endpoints Declared

This report lists all patients who have a primary endpoint declared on E01, E02 or E03. Patient number, initials, the declared event and the date are listed. Information is displayed in patient number order.

This report identifies patients who have more than one endpoint declared.

24. Quarterly Missed Visits

This report provides a list of randomized patients for whom at least one quarterly visit was missed. For each missed visit, the report lists the patient number, initials, the month of the missed visit, the target date of the missed visit, whether a Missed Follow-Up Visit Report (Form F04) was completed, and whether the patient was classified as inactive on that Missed Visit Report. The report will be printed in patient order. For patients that have become inactive or died, missed quarterly visits will need to be accounted for (and will be printed) until the inactive status is reported on the Missed Visit Report (Form F04).

This report can help to identify patients that may be rendered as inactive. It can help to be sure that all necessary Forms F04 (Missed Visit Report) are completed.

25. Quarterly Visit Attendance

This report provides information similar to what the Biostatistical Coordinating Center distributes in the Steering Committee report. This report lists for all clinic patients: study status according to the status database (active/inactive), number of follow-up weeks since randomization and randomization date. Additionally, for each quarterly visit: if the visit occurred, if the visit was missed, or if the visit window is still open.

This report can be generated for all patients within a chosen patient number range, or only for those patients who missed two or more visits. When a patient has missed two or more consecutive quarterly visits, the patient should be reported as inactive in the status database. Additionally, this report can help identify visits missing an F form.

26. Randomized Patients Form Labels

This report provides a mechanism for printing form labels for randomized patients. Labels include the patient number, initials, date of birth, AUA 4 Point Event flag, and Creatinine Rise Event flag. They are to be placed over the patient identification section of each form.

When a patient is randomized, a page of labels should be printed. Subsequent copies can be printed as needed. The labels for this report will be the clinic's responsibility to supply. The correct labels to use in the hp Laserjet printer are 1" x 2-5/8" made by Avery (# 5160), Office Essentials, and several other companies. The labels must be inserted into printer with the label side facing toward the individual.

27. Reasons for Exclusion from Randomization

This report is generated for all screened patients with a Screening Visit 1 during a selected time period. For each reason for exclusion, the number of individuals excluded is displayed by ethnic group. Please note there may be multiple exclusions for a single patient.

This report can be helpful in monitoring reasons patients were excluded.

28. Recruitment Source Summary

This report lists the number of individuals recruited from the various sources according to data entered on the Recruitment Source Tracking Information (Form T02). This report also lists the number of patients randomized by recruitment source.

29. Schedule of Follow-up Visits - Calendar

This report generates a patient calendar. (**Note:** this is only for randomized patients, screening numbers are not accepted). Only one month can be printed per page. Up to 12 months can be printed at a time.

Two of the abbreviations used on the calendars are: "Wk" for Week Number and "SFV-M X" for the window for the Scheduled Follow-up Visit for Month X.

30. Schedule of Follow-up Visits - Listing

This reports provides a list of the scheduled follow-up visits for a particular patient. The report lists the type of visit, target date and window. This report can be run for a selected range of patients and visit dates.

31. Screened Patients Not Excluded or Randomized

This report provides a list of all patients with a Screening Visit 1 Inventory (Form B02) that have not yet been randomized according to the Randomization Information (Form B04) or excluded according to the Eligibility and Exclusion Inventory (Form B01). The report lists screening number, initials, Screening Visit 1 visit date, and the deadline for the randomization (end of 42 day period).

32. Visits and Medication Status Over Time

This report provides four optional methods for listing visits and medication status over time. Reports can be generated for active patients who have discontinued one or more medications, active patients not seen in >150 days, inactive patients or all of the above. This report can be run for a selected range of patients.

This report can be helpful in identifying discrepant medication information, dose information, and active/inactive status information for a patient.

THEME AUDITS

Theme audits are designed to help each clinic resolve discrepancies found within their clinic data. Although official theme audits are generated by the BCC, it is possible to check the status of some of the theme audits at the clinic. Theme audits can be generated by selecting the MTOPS theme audits icon located in the MTOPS system group or by the theme audits button located at the top of the data entry screen. An individual audit can be selected or the "All theme audits" listing which generates all audits listed.

These audits can be helpful in cleaning up the data in addition to the BCC's distribution.

STATUS DATABASE

The Status Database is designed to help each clinic and the BCC keep track of the status of each randomized patient. The database will be partially generated automatically, and partially entered by clinic staff on the clinic microcomputer.

The automatically generated fields cannot be altered (those displayed in the red area). These fields are: patient number, screening number, patient initials, patient date of birth, randomization date, last visit date (from forms B04, F01, F03, and F06), type of last visit (titration, standard, major, interim) and number of days since last visit. These are items which are imported from the data and will be automatically entered into the Status Database whenever the database is accessed or printed. Therefore all information in these fields accessed or printed will be up-to-date.

All other fields will be **UPDATED BY CLINIC STAFF**. These fields are: follow-up status (**Active** or **Inactive**), use of coded doxazosin (**Yes** or **No**), use of coded finasteride (**Yes** or **No**), progression of BPH (**Yes** or **No**), crossover to known invasive therapy (**Yes** or **No**), prostate or bladder cancer (**Yes** or **No**), abbreviated protocol (**Yes**, **No**, or **Limited**), and mortality (**Yes** or **No**). The fields have defaults for the patient having Active status, Yes using doxazosin, Yes using finasteride, No progression, No crossover, No prostate or bladder cancer, No abbreviated protocol, and No mortality. Only the patients who no longer fit these status defaults must be updated.

Note: The limited option for abbreviated protocol refers to a patient who has undergone a cystectomy for bladder cancer and follow-up is limited to the MOS-36 Health Survey administered at annual visits.

The database will be automatically printed weekly with up-to-date information. It may also be printed at any time. The reports printed include an Active Patients Report, an Inactive Patients Report, a Discrepancy Report, and a Summary Report.

CLINIC STAFF DATABASE

The Clinic Staff Database is designed to help the BCC and NIH to keep track of staffing at each clinic. The database should be updated each month.

The Clinic Staff Database is available from two places: the MTOPS system group, and a button within the main screen of the MTOPS Data Entry software.

Once selected, the following menu appears:

```

      MTOPS
CLINIC STAFF DATABASE

      Add New Record
      Modify Record
      Remove Record
      View Current Staffing
      Print Staff Information
      Quit

```

When *Add New Record* is selected, the following panel appears to enter staff information into:

```

      MTOPS
CLINIC STAFF DATABASE - ADD NEW RECORD

TITLE:                (Use F9 key to display position titles)
NAME:
% FTE:
DESCRIPTION:

```

Use the F9 key to pull up the position title list. One of the titles available in the list must be used. All information is required except the description. The description should be used for clinic purposes (e.g. maternity leave, job responsibilities, etc.).

Clinical Research Center (CRC) Staff

If the clinic is assisted by a CRC, this should be documented in the Clinic Staff Database. Select **CRC Staff** as the job title and type **CRC Staff** as the name (name cannot be left blank). Then enter the estimate for % FTE contribution that the CRC provides. Note that this number may be > 100%.

```

Use the following directional keys for navigating within these
screens:
Page Down will display the next screen (if there is more data) or
exit if it is the last screen.
Page Up will display the previous screen, for all screens after the
first.
The F9 key moves the cursor to the next record on the screen. If
used on the last record on the screen, it loops back up to the top.
The F8 key moves the cursor to the previous record on the screen. If
used on the first record on the screen, it loops back down to the
bottom.

```

When *Remove Record* is selected, a screen appears listing the names of all staff members currently on file in the clinic's

staff database with a number to identify the record. From this list, enter the number of the clinic staff person to be removed from the database. A panel with the individual's information will appear and a confirmation to delete the record.

When **View Current Staffing** is selected, all information entered in the database can be viewed, seven staff members per screen. The total number of FTE is listed at the end of the staff member information.

When **Print Staff Information** is selected, all the current staff information is displayed on the screen, with the following prompt:

Do you want a printed copy of this information? (Y/N)

PAC REPORTS

The PAC Reports Software is available from two places: the MTOPS group, and a button within the main screen of the MTOPS Data Entry software.

Once selected, the following menu appears:

```
MTOPS STUDY
PAC REPORTS

Enter Inactive Patient Information
Liaison Reports to Print
Quit
```

When **Enter Inactive Patient Information** is selected, the patient numbers of all patients currently inactive appear.

```
MTOPS INACTIVE PATIENTS

05244
05253
05255
05335
05354
05364
QUIT

Use Arrow Keys to move between patients, ENTER to Select, QUIT
to Exit
```

The UP and DOWN arrow keys allow movement from patient to patient. Once the desired patient number is selected,

press the ENTER key. This displays the following screen:

```
PATIENT: 05244          INITIALS: ABCD  
LAST VISIT DATE: 01/04/97  
  
ADDED: 04/01/99  COMMENTS FIRST ENTERED: 04/01/99  
LAST UPDATED:   /   /  
CONTACT: 4/1/99 Phoned patient's home. Wife answered, said  
patient out of state due to chronic illness in family, will be  
out of state for undetermined period  
OUTCOME: Told wife to tell patient we are wondering how he is  
doing w/urinary problems & if they had gotten worse to phone us  
collect.  
PLAN: Plan to call again next month 5/3/99. Hopefully patient  
will be back in town by then.  
  
ADDED: 05/03/99  COMMENTS FIRST ENTERED:   /   /  
LAST UPDATED:   /   /  
CONTACT:  
OUTCOME:  
PLAN:  
  
F10 to copy previous Contact/Outcome/Plan, Page Down to Exit
```

The only information that can be modified is information pertaining to the current month. Information from previous months may be viewed, but cannot be altered. For example, at any time during the month of May 1999, information regarding the contact, outcome, and plan may be altered for an individual for May of 1999. Any information for April 1999 or any other past month during which the patient was inactive cannot be altered. Once May ends and June begins, May information may only be viewed and can no longer be changed.

The F10 key will copy the Contact, Outcome, and Plan from the previous month. This comes in handy when last month's information needs to be reiterated. Once the information is copied, then it can be altered as necessary to reflect any changes since the previous month.

When *Liaison Reports to Print* is selected, the following menu of reports will appear:


```

                                MTOPS STUDY
                                PAC REPORTS - LIAISON REPORTS TO PRINT

                                Inactive Patient Log
                                Inactive Patients Not Entered This Month
                                Inactive Patients Report to Liaison
                                Patients Not Seen in > 150 Days Report to Liaison
                                Quit

```

When *Inactive Patient Log* is selected, the following screen appears:

```

                                INACTIVE PATIENT LOG

                                INACTIVE STATUS (Choose one)
                                Currently Inactive      Y
                                Inactive at any time    N

                                HISTORY PER PATIENT (Choose one)
                                Most Recent Six Months Y
                                Entire                  N

                                PATIENT RANGE: 01001 - 18999

                                (Enter parameters or ESC key to quit)

```

Several options may be selected in the Inactive Patient Log. These include patients inactive status, history per patient and a patient range. The default parameters include the most recent six months of information for all currently inactive patients.

Once the desired parameters have been selected, press ENTER. All pages of the report appear on the screen, and clinic staff can choose to print the information or not.

When *Inactive Patients Not Entered This Month* is selected, the following screen appears:

```

The following patients are currently considered inactive and the
inactive patient log has not been updated yet this month for them:

05244          05335
05253          05354
05255          05364

Do you want a printed copy of this information (Y/N)?

```

Choosing Y produces a printed list of these patients with their initials. This report will automatically print on the 21st of each month. This allows time to enter the information for them before the end of the month.

When **Inactive Patients Report to Liaison** is selected, the computer generates a printed summary that lists all inactive patients, their initials, and the date of their last visit (see below). **Note:** This is a modified version of the report that was previously located in the reports menu, and will automatically print on the 1st of each month.

MTOPS			
INACTIVE PATIENTS REPORT TO LIAISON			
UNIVERSITY OF...			
Total Number of Inactive Patients: 6			
The following patients are currently considered as inactive. They must be contacted as per the guidelines. This report must be completed and faxed to your Protocol Adherence Committee (PAC) liaison by the end of the month with the individual patient logs.			
Patient Number	Initials	Date of Last Visit	
* 05244	ABCD	01/04/97	
05253	EFGH	10/01/98	
# 05255	IJKL	01/01/99	
* 05335	MNOP	12/10/96	
05354	QRST	05/25/97	
05364	UVWX	07/06/97	
* This patient has missed 2 or more quarterly visits, but the status database indicates he is active. Please change status database.			
# This patient is new to the list since last month.			

When **Patients Not Seen in > 150 Days Report to Liaison** is selected, the computer generates a printed list (see below). **Note:** This is the same report that was previously located in the reports menu. This report automatically prints every Sunday night.

**MTOPS
PATIENTS NOT SEEN IN >150 DAYS REPORT TO LIAISON
UNIVERSITY OF...**

The following active patients have not been seen in >150 days and must get urgent attention (see guidelines). This report must be completed and faxed to your Protocol Adherence Committee (PAC) liaison by Friday afternoon.

Patient #	Initials	# Days since last visit	Date patient becomes inactive	Contact, Outcome, and Plan for next contact
05123	SUSC	182	04/24/99	C _____ O _____ P _____
05139	JASM	194	05/12/99	C _____ O _____ P _____

REFERENCES

- Abrams PH, Griffiths DJ. The assessment of prostatic obstruction from urodynamic measurements and from residual urine, *British Journal of Urology* 51:129-134, 1979.
- Agresti A. *Categorical Data Analysis*. New York, Wiley, 1990.
- Buckley IV, James I. Linear regression with censored data. *Biometrika*, 66:429-436, 1979.
- Conover WJ. *Practical Nonparametric Statistics*. New York, Wiley, 1980.
- DeMets D, Hardy R, Friedman L, Lan KKG. Statistical aspects of early termination in the beta-blocker heart attack trial. *Controlled Clinical Trial*, 5:362-372, 1984.
- Friedman B. A simple urn model, *Communications of Pure and Applied Mathematics* 2:59-70, 1949.
- Gastwirth JL. The use of maximum efficiency robust tests in combining contingency tables and survival analysis. *Journal of the American Statistical Association*, 80:380-384, 1985.
- Griffiths D, Van Mastrigt R, Bosch R. Quantification of urethral resistance and bladder function during voiding, with special reference to the effects of prostate size reduction on urethral obstruction due to benign prostatic hyperplasia, *Neurourologic Urodynamics* 8:17-27, 1989.
- Griffiths DJ. Assessment of detrusor contraction strength of contractility, *Neurourologic Urodynamics* 10:1-18, 1991.
- Halperin M, Lan KKG, Ware JH, Johnson NJ, DeMets DL. An aid to data monitoring in long-term clinical trials. *Controlled Clinical Trials*, 3:311-323, 1982.
- Hardy RJ, Davis BR, Palmer EA, Tung B, on behalf of the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Statistical considerations in terminating randomization in the multicenter trial of cryotherapy for retinopathy of prematurity. *Controlled Clinical Trials*, 12:293-303, 1991.
- Harrington DP, Fleming T. A class of rank test procedures for censored survival data. *Biometrika*, 69:553-566, 1982.
- Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika*, 75:800-802, 1988.
- Holm S. A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics*, 6:65-70, 1979.
- Jennrich RI, Schluchter MD. Unbalanced repeated-measures models with structured covariance matrices. *Biometrics*, 42:805-820, 1986.
- Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. New York: John Wiley, 1980.
- Lachin JM. Some large-sample distribution-free estimators and tests for multivariate partially incomplete data from two populations. *Statistics in Medicine*, 11:1151-1170, 1992.
- Lachin JM, Foulkes MA. Evaluation of sample size and power for analyses of survival with allowance for nonuniform patient entry, losses to follow-up, noncompliance, and stratification. *Biometrics*, 42:507-519, 1986.
- Lachin JM, Lan SP, and The Lupus Nephritis Collaborative Study Group. Termination of a clinical trial with no treatment

- group differences: The lupus nephritis collaborative study. *Controlled Clinical Trials*, 13:62-79, 1992.
- Lachin JM, Wei LJ. Estimators and tests in the analysis of nonindependent 2x2 tables with partially missing observations. *Biometrics*, 44:513-528, 1988.
- Laird NM and Ware JH. Random-effects models for longitudinal data. *Biometrics*, 38:963-974, 1982.
- Lan KKG and DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika*, 64:191-199, 1983.
- Lan KKG, Lachin JM. Implementation of group sequential logrank tests in a maximum duration trial. *Biometrics*, 46:759-770, 1990.
- Lan KKG, Rosenberger WF, Lachin JM. Use of spending functions for continuous or occasional monitoring of data in clinical trials. *Statistics in Medicine*, 12:2219-2231, 1993.
- Lan KKG, Simon R, Halperin M. Stochastically curtailed tests in long-term clinical trials. *Communications in Statistics*, 1:207-219, 1983.
- Lan KKG, Wittes J. The B-value: A tool for monitoring data. *Biometrics*, 44:579-585, 1988.
- Liang K, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika*, 73:13-22, 1986.
- McCullagh P. Regression models for ordinal data. *Journal of the Royal Statistical Society*, 42:109-142, 1980.
- Miller RG. *Simultaneous Statistical Inference*. New York, Springer-Verlag, 1981.
- Miller RG. *Survival Analysis*. New York: John Wiley, 1981.
- National Institutes of Health (NIH). Clinical trials activity. *N.I.H. Guide for Contracts and Grants*. 8:29, 1979.
- O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*, 35:549-556, 1979.
- Tarone RE and Ware J. On distribution-free tests for equality of survival distributions. *Biometrika*, 64:156-160, 1977.
- Wei LJ. The accelerated failure time model: A useful alternative to the Cox regression model in survival analysis. *Statistics in Medicine*, 11:1871-1879, 1992.
- Wei LJ, Lachin JM. Properties of urn randomization in clinical trials, *Controlled Clinical Trials* 9:345-364, 1988.
- Wei LJ and Lachin JM. Two-sample asymptotically distribution-free tests for incomplete multivariate observations. *Journal of the American Statistical Association*, 79:653-661, 1984.
- Zucker DM, Lakatos E. Weighted log rank type statistics for comparing survival curves when there is a time lag in the effectiveness of treatment. *Biometrika*, 77:853-864, 1990.

Third Edition Update: February 20, 2001

APPENDIX

STATEMENT OF VOLUNTEER CONSENT
FOR
The National Institutes of Health
Treatment of Benign Prostatic Hyperplasia
Study Patient Rights

You are being asked to participate in a research study. Persons who participate in research are entitled to certain rights. These rights include but are not limited to your right to:

1. Be informed of the nature and purpose of the research;
2. Be given an explanation of the procedures to be followed in the research, and any drug or device to be utilized;
3. Be given a description of any attendant discomforts and risks reasonable to be expected, if applicable;
4. Be given a disclosure of any benefits to the subject reasonable to be expected, if applicable;
5. Be given a disclosure of any appropriate alternatives, drugs, or devices that might be advantageous to the subject, their relative risks and benefits;
6. Be informed of the alternatives of medical treatment, if any, available to the subject during or after the experiment if complications arise;
7. Be given an opportunity to ask any questions concerning the research and the procedures involved;
8. Be instructed that consent to participate in the research may be withdrawn at any time, and the subject may discontinue participation without prejudice;
9. Be given a copy of the signed and dated consent form;
10. And be given the opportunity to decide to consent or not to consent or participate in research without the intervention of any element of force, fraud, deceit, duress, coercion or any undue influence of the subject's decision.

STATEMENT OF VOLUNTEER CONSENT
FOR
The National Institutes of Health
Treatment of Benign Prostatic Hyperplasia

INTRODUCTION: You are suffering from a urinary obstruction caused by an enlargement of your prostate. This disease is a non-cancerous condition called benign prostatic hyperplasia (BPH). BPH is a condition characterized by trouble with urination caused by enlargement of your prostate gland. There are two drugs that doctors think may effectively treat your prostate condition. These are doxazosin and finasteride. You are being asked to participate in a study that is intended to provide important information about the effectiveness of these drugs for treating BPH.

Approximately 2,800 patients 50 years of age and older will participate in the study nationwide.

PURPOSE: The purpose of this study is to determine whether doxazosin, finasteride, a combination of doxazosin and finasteride, or a placebo (inactive medication) is effective in treating BPH and whether or not these drugs delay or prevent the progression of BPH. Doxazosin relaxes and reduces the tension in the smooth muscle of the prostate gland. Finasteride reduces the size of the prostate gland. BPH and its symptoms are thought to be caused, at least in part, by prostate muscle tension and enlarged prostate size. The results of this study should provide meaningful information about the effects of these drugs on the pattern of prostate growth.

Doxazosin (Cardura) is currently approved by the United States Food and Drug Administration (FDA) for symptomatic BPH. It may also be used for the treatment of high blood pressure. Finasteride (Proscar) has also been approved by the FDA for the treatment of symptomatic BPH. Neither drug has not been approved for use in combination for the treatment of symptomatic BPH.

The experimental aspect of this study is the combination of these drugs to treat your prostate condition and to determine whether or not they delay or prevent the condition from worsening.

Several studies have shown that doxazosin or finasteride when taken by themselves, are effective in the treatment of BPH and its symptoms. There are however no completed studies to test the combination of these drugs or to compare their effectiveness.

PROCEDURES: Before beginning treatment (medication), you will need to complete several tests for a baseline evaluation. These tests are obtained in order to provide evidence that the problems you experiencing are caused by BPH.

At the first visit your vital signs will be taken (blood pressure and pulse) and you will be given a

complete physical examination including a rectal examination. 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.

You will complete four questionnaires that determine the severity of your urinary symptoms, your sexual health and your quality of life. The force of your urinary stream will be measured (uroflowmetry). This is done by urinating into a basin attached to a machine which records the volume and speed of your urine flow. Uroflowmetry will be carried out in such a way as to ensure your privacy.

The amount of urine remaining in your bladder after urinating (post void residual [PVR]) will then be determined using ultrasonography (sound wave). A probe is placed on your lower abdomen so that the sound waves can determine the amount of fluid (urine) left in your bladder. This procedure has no risks and is painless.

Approximately 1 ounce of blood will be drawn for routine laboratory tests. The blood tests drawn will include a Complete Blood Count (CBC) and Blood Chemistry which are used to evaluate your general health, and a Prostate Specific Antigen (PSA) level, which is used to help measure prostate health.

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 using 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.

If all of the above tests indicate that you are eligible, then you will be started on study medication. You will be given either 1) doxazosin and placebo, 2) finasteride and placebo, 3) doxazosin and finasteride, or 4) two placebos (an inactive medications) to take for a period not to exceed six years. All patients will receive placebo at some time during the study and some patients will receive placebo during the entire study. The choice of which type of medication you receive will be determined by chance. The study is designed so that neither you nor the investigator will know what treatment group you are assigned to. However should this information become medically necessary, it could be immediately obtained. This blinding is to assure that the four treatments are evaluated in an unbiased manner.

During this six year period you will return for 4 visits each year. At each of these visits you will be asked to complete a questionnaire about your urinary symptoms.

Your vital signs will be taken (blood pressure and pulse) and the force of your urinary stream and post void residual will also be measured at each one of these visits as described above. In addition, at 6 months and then every year blood will be drawn as described above. Every year you will be asked to complete

a questionnaire about your sexual health.

RISKS: You have been informed of the discomforts and risks which can be reasonably expected as part of the study. This includes slight discomfort with placement of the ultrasound probe during the prostate ultrasound.

A small amount of pain and bruising may be associated with blood drawing. An elevated PSA level may be a sign of an unhealthy prostate. Because finasteride reduces the size of your prostate, it will cause a lowering of your PSA level. Doctors are uncertain whether this will interfere with the use of this test to diagnose prostate cancer. The PSA alone does not indicate the presence or absence of prostate disease. As a participant in this study, you are having all standard tests and procedures used to determine the health of your prostate including a digital rectal exam. If you need any further explanation, you are free to ask your physician.

As doxazosin is also used for the treatment of high blood pressure, certain side effects may occur during this study. Based on past experience of other people who have received doxazosin for high blood pressure include: headache, nausea, palpitations (irregular heartbeat), swelling of the legs, and fatigue. In addition, low blood pressure causing dizziness, postural dizziness, and/or fainting may occur. Study personnel will explain the proper precautions to be taken in order to avoid these latter symptoms.

Certain side effects and discomforts associated with finasteride may occur. Side effects previously reported in a small portion of persons taking this drug (3 to 4%) include impotence, decreased libido, and decreased ejaculate volume. Other rarely occurring side effects include breast swelling and/or tenderness and allergic reactions such as lip swelling and rash.

It is not known whether the amount of finasteride that could potentially be absorbed by a pregnant woman through either direct contact with crushed finasteride tablets can adversely affect a developing male fetus. Therefore, because of the potential risk to a male fetus, a woman who is pregnant or who may become pregnant should not handle crushed finasteride tablets.

The study medication should not be taken by anyone other than the person that it was prescribed for, and it should be kept out of the reach of children or others who have a limited ability to read or understand.

It is possible that your urinary symptoms and the obstruction from the enlarged prostate may progress during the study resulting in further blockage of the urinary flow and or a urinary tract infection. In the event that these occur, you may be withdrawn from the study medication(s).

You will be told of any significant new findings developing during the course of this study which may relate to your willingness to continue participation.

COMPENSATION FOR INJURIES: By consenting to participate in this study, you agree to take the risks listed above. If unexpected injuries related to this study which are not discussed in the paragraph entitled "Risks" occur, (...name of institution conducting study...) will provide you humanitarian emergency care without charging you a physician's fee for such treatment. Such free care does not mean that negligence has occurred.

BENEFITS: The information which is obtained in this study may be scientifically useful and possibly helpful to others. Your participation in this study might benefit you, if you are on the study medication and the study medication is found to be effective, by helping you void with a better stream with less symptoms and may reduce the blockage. If successful, there may be less risk to your bladder and kidneys for developing infection or damage. For patients assigned to the study medication, another potential advantage is avoiding surgery for BPH. However, no benefit can be guaranteed. You will also be helping future patients by providing important information on the treatment of BPH.

ALTERNATIVE PROCEDURES: The only Food and Drug Administration approved methods for treating BPH are surgery (which does not always produce a permanent improvement in symptoms and can be associated with significant complications) Proscar, Cardura or another medication, Hytrin. These medications for treating your prostate are all available in your drugstore. Other treatments available are all experimental and include other drugs, lasers, placement of a coil in the prostate channel or hyperthermia.

Another alternative would be to not participate in this study, or to live with these symptoms without pursuing treatment at this time (watchful waiting).

FINANCIAL BENEFITS/RISKS: Some third party payers (insurance companies, HMO's etc.) may not pay for hospitalization, treatments or procedures which are determined to be experimental. All costs not paid by your insurance will be your own financial responsibility. However, all study related clinic visits, laboratory and procedure costs as well as physician fees will be waived.

NO PREJUDICE: Your decision about whether or not to participate in this study will not prejudice your present or future relationship with (name of institution conducting study) or the staffs of these institutions; nor will it influence the quantity or quality of care to which you entitled. If you decide to participate, you are free to withdraw at any time without judgment. However you must immediately inform the study physician or nurse of this decision. Withdrawing will not in any way affect the nature of the care or treatment otherwise available to you. You may contact the Chairman of the Human Research Review Committee of (name of

institution) at phone # for further information related to any aspect of this research and your rights as a study participant.

WITHDRAWAL / TERMINATION: The physician in charge of the study can remove you from the study with or without your consent if in his/her judgment it is in your best interest to improve your medical care, or if you fail to follow the study schedule.

CONFIDENTIALITY: All information from this investigation that can specifically identify you will remain confidential and will only be available to persons connected with this study. Scientific data or medical information resulting from this study that does not identify you may be presented at meetings and published so that the information can be useful to others. You also authorize the United States Food and Drug Administration (FDA) to have access to your records concerning this research project.

ANSWER INQUIRIES: Dr./Ms./Mr. _____ has explained the above matters to you and you understand that explanation. (S)he has offered to answer your questions concerning the procedures involved in this study. If you have further questions concerning this project at any time, you are free to ask them of (full name of investigator) at phone # during the day and phone # after hours.

**The National Institutes of Health
Treatment of Benign Prostatic Hyperplasia**

I understand that this program will be under the supervision of _____ (name of investigator) or another professional person who is designated to assist or act for him.

I, _____ hereby agree to participate in the investigation entitled "Treatment of Benign Prostatic Hyperplasia". I have read or have had read to me all of the above. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other treatment choices available to me.

I understand my rights as a research patient and I voluntarily consent to participate in this study. I understand what the study is about, and how and why it is being done. I will receive a signed copy of this consent form.

Signature of Subject or Authorized Representative Date

Signature of Witness Date

I have defined and fully explained the study as described herein to the study participant.

Type or Print _____
Name of Principal Investigator or Authorized Representative

Type or Print _____
Position Title

Signature Date

NIH-BPH CLINICAL TRIAL
 EDIT REPORT FOR: SCREENING VISIT 1 INVENTORY
 (FORM B02.2)

CLINIC	SCREENING NUMBER S0010
VISIT DATE 01/31/96	PATIENT ID NUMBER ----
FORM COMPLETED BY	DATE FORM EDITED BY BCC 02/13/96
ENTERED OR LAST MODIFIED ON 02/06/96	BATCH ID 588704

QUESTION	VARIABLE DESCRIPTION	VARIABLE NAME	FORM VALUE	REVISED VALUE	CHECK IF VALUE OK
----------	----------------------	---------------	------------	---------------	-------------------

F 2c. STAND BP DIAST 2	SBPSD2	_____	()
------------------------	--------	-------	-----

PROBLEM: MISSING VALUE
 COMMENT: KNOWN PERMANENTLY MISSING OR INVALID RESPONSE

F 2d STAND HEART RATE 2	SBPSHR2	_____	()
-------------------------	---------	-------	-----

PROBLEM: MISSING VALUE
 COMMENT: KNOWN PERMANENTLY MISSING OR INVALID RESPONSE

G 1 ORTHOSTATIC HYPOTENSION ?	SORTHYP	_____	()
-------------------------------	---------	-------	-----

F 1a SUPINE BP SYST	SBPLS	_____	()
---------------------	-------	-------	-----

F 1a. SUPINE BP DIAST	SBPLD	_____	()
-----------------------	-------	-------	-----

F 2a STAND BP SYST 1	SBPSS1	_____	()
----------------------	--------	-------	-----

F 2a. STAND BP DIAST 1	SBPSD1	_____	()
------------------------	--------	-------	-----

F 2c STAND BP SYST 2	SBPSS2	_____	()
----------------------	--------	-------	-----

F 2c. STAND BP DIAST 2	SBPSD2	_____	()
------------------------	--------	-------	-----

PROBLEM: INCONSISTENT WITH OTHER DATA ON THIS FORM
 COMMENT: KNOWN PERMANENTLY MISSING OR INVALID RESPONSE

H 1 HEIGHT IN INCHES	SPEHT	_____	()
----------------------	-------	-------	-----

PROBLEM: MISSING VALUE
 COMMENT: KNOWN PERMANENTLY MISSING OR INVALID RESPONSE

MTOPS
THEME AUDIT
DISCREPANT DATES FOR BIOPSIES PERFORMED
FORM P01 AND INFORMATION FAXED TO THE DIAGNOSTIC CENTER
AS OF MAY 12, 1997

----- CLINIC NUMBER=0 -----

SCREENING NUMBER	PATIENT NUMBER	TYPE OF VISIT	DATE OF VISIT	DATA SOURCE
S0054	00116	SCREENING	06/24/96	P01 COMPLETED
S0054		END OF STUDY	07101/96	DIAG CENTER

Requisition Form (MTOPS)

This Form is for ordering more copies of packets or forms. Allow approximately 2 weeks for delivery.

Date: _____

TO: Monica Fields
 FAX # (301) 881-3589

From: _____ Clinic # _____

	# of Copies		# of Copies
1st Year Packet	_____	Binders/envelopes (boxes of 12)	_____
Screened/not Randomized Packet (SV 1)	_____	BCC Labels	_____
Forms for SV2	_____	Coord return labels	_____
Add. Year Packet	_____		

Additional Forms

(Please indicate Spanish or Interview version if applicable.)

Form #	# of Copies	Form #	# of Copies
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

Fax Transmission

The Biostatistical Coordinating Center - MTOPS

6110 Executive Blvd #750 Rockville, MD 20852 301-881-9260 FAX:301-881-3589

To: _____ From: _____

COMPUTER SYSTEM PROBLEM / REQUEST LOG

Date:

--	--	--	--

CENTER NUMBER

--	--

CENTER NAME _____

Check: Problem OR Request

Form or Report Number _____

Describe problem or request in detail

AN ERROR HAS OCCURRED! Contact Technical Support Reference # _____ Error _____
Program _____ (_____) Quit
If an error box appears as shown above, please copy the information to this box.

FOR BCC USE ONLY							
RECEIVED: DATE <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td></tr></table>				TIME <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td style="width: 30px; height: 20px;"></td><td style="text-align: center;">:</td><td style="width: 30px; height: 20px;"></td></tr></table>		:	
	:						
REPLY _____							

MTOPS

AGENT REQUEST FORM

Instructions: Type or print clearly all information except signature. Complete all sections except for box labeled **McKesson Use**. Sign the form in the space provided. All orders received by 2:00 pm EST weekdays will be shipped to arrive 2nd business day by 4:30 pm. If drug is needed overnight, check "Yes" in the Overnight field. If an overnight shipment is needed for Saturday and clinic personnel will be available to receive it, check "Yes" in the Saturday field.

FAX or Express Mail to: McKesson BioServices 625-C Lofstrand Lane Rockville, MD 20850 FAX: (301) 738-2478 Phone: (301) 762-0069	Clinic Number:		McKesson Use Order # _____
	Clinical Investigator's Name:		
	Ordered by:		
	Telephone number:		
	Date ordered:	Date needed by:	
	Overnight: () Yes	Saturday: () Yes	

IND Number	Patient # (Range)	Agent Name	Strength	Quantity	Comments	
43,564		Run-in Kits Doxazosin (20 Tab/Bot)				
		Finasteride (20 Tab/Bot)	N/A			
		Titration Kits Doxazosin (5 Bottles)				
		(Doses A, B, C, D, and C)	N/A	1 Kit/Pt.		
		Treatment Kits Finasteride (120 Tab/Bot)	N/A			
		Doxazosin (120 Tab/Bot)	Dose C			
		Doxazosin (120 Tab/Bot)	Dose D	1 Kit/Pt.		

TYPE Pharmacy Shipping Address Below: (No P.O. Box Numbers)

Authorized Signature Date

MTOPS

AGENT RETURN FORM

RETURN ONLY AGENTS SUPPLIED BY McKESSON BIOSERVICES

The Agents listed below were returned by: _____

Address: _____

INSTRUCTIONS FOR INVESTIGATOR

1. Type or print clearly all information-one item per line. Fill in all sections.
2. **DO NOT** marked in the shaded area.
3. Sign and date list.
4. Pack the agents well to minimize breakage and leakage.
5. Enclose the completed list with the agents and return to:
 MTOPS
 c/o McKesson BioServices
 625-C Lofstrand Lane
 Rockville, MD 20850

Agent Name	Full / Partial	Quantity	Patient # (Range)	For McKesson BioServices Use Only	
				Rec. Code	Received by:
					Checked by:
					Date:

To be completed by site

Individual preparing this list:
 (if other than the investigator)

 Name

 Signature

 Title

 Telephone No.

Comments: _____

MTOPS

Investigational Drug Accountability Record

Page No. _____

Name of Institution

IND No.

43,564

Drug Name, Dose Form and Strength

Protocol Title

Investigator

Date	Patient's Name	Patient's Number	Dose	Quantity Dispensed or Received	Balance Forward	Manufacturer and Lot No.	Recorder's Initials
					Balance		

MTOPS DIAGNOSTIC CENTER REQUISITION FORM

Please fill out one form per patient and FAX to (303)316-9084 before sending specimens

Site ID# _____ Patient ID# _____ Initials _____

Patient Screening# _____

Visit Type:

Annual ____ End of Study ____

Specimen Collection Date: ____ / ____ / ____

Other: _____

FEDEX Shipping Information

Dry ice package airbill# _____

Shipping Date ____ / ____ / ____

Formalin package # _____

Test(s) Order

Serum

(Office use only)

- Prostate Specific Antigen (PSA Hybritech)
- Archival Tubes
- Dihydrotestosterone (DHT)
- Testosterone/Luteinizing Hormone (LH)

Biopsy

- Formalin Bx (LTZ____ RTZ____ LPZ____ RPZ____ other: _____)
- Frozen Bx (LTZ____ RTZ____ other: _____)

Supply Order

(Please write QUANTITY needed and allow about 2 weeks for delivery)

Number

(Office use only)

- PSA/Archive serum kits
- Hormone (Testosterone, LH, DHT) serum kits
- Free/Total PSA serum kits
- Zip-lock bags (small) for frozen biopsy cores
- White formalin biopsy specimen boxes w/ foam insert & 4 vials
- Styrofoam dry ice shipping containers *(allow extra time)*
- OCT freezing medium
- Cryo-molds (box of 100)
- Green biopsy ink
- Biopsy sponges (bag of about 50)
- Wooden sticks
- Other: _____

MTOPS Diagnostic Center Information

General phone number: (303)316-9130

Shipping Address:

Prostate Diagnostic Lab, 4525 E 8th Ave, Denver, CO 80220

Contacts:

Kathleen Torkko (303)316-9258; pager (303)266-9267

Ginger Johnson (303)316-9158; pager (303)266-2385

MTOPS DIAGNOSTIC CENTER REQUISITION FORM
FREE/TOTAL PSA

Please fill out one form per patient and FAX to (303)316-9084 before sending specimens

Site ID# _____ Patient ID# _____ Initials _____

Patient Screening# _____

Specimen Collection Date: ____ / ____ / ____

FEDEX Shipping Information

Shipping Date ____ / ____ / ____ Dry ice package airbill# _____

Test Ordered (serum)

Free/Total PSA

Instructions:

This test is available only when annual visit PSA is found to be borderline for suspicious, *i.e.*, between 4 and 10 ng/ml.

Collect at least 2 ml blood in a red top tube. Allow to clot and separate as usual. Transfer 1 ml serum into clear plastic tube. Label with green f/t PSA label (be sure to include PtID# and collection date on label). Place tube with serum into plastic bag and freeze until shipped. Ship as usual on dry ice.

MTOPS Diagnostic Center Information

Shipping Address: Prostate Diagnostic Laboratory
4525 E. 8th Ave., Denver, CO 80220
(303)316-9130

Contacts: Kathleen Torkko (303)316-9258; pager (303)266-9267
Ginger Johnson (303)316-9158; pager (303)266-2385