

AD _____

Award Number: DAMD17-02-1-0040

TITLE: Effects of Androgen Blockade on Cognitive Function and
Quality of Life in Men with Prostate Cancer

PRINCIPAL INVESTIGATOR: James P. Grigsby, Ph.D.

CONTRACTING ORGANIZATION: University of Colorado Health Sciences Center
Aurora, Colorado 80045-0508

REPORT DATE: February 2003

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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13. ABSTRACT (Maximum 200 Words) The purpose of this project is to examine the nature and severity of cognitive impairments experienced by men undergoing continuous androgen deprivation or intermittent androgen deprivation treatment. The cognitive abilities of androgen deprivation patients will be compared with those of a sample of healthy men. We are undertaking collection of data from three groups: 35 men on intermittent androgen deprivation therapy, 35 men on continuous androgen deprivation therapy, and an age- and education-matched sample of 35 healthy (cancer-free) men. Our major hypothesis is that patients undergoing androgen deprivation therapy will experience impairments in those cognitive abilities reported in the research literature to be related to androgen levels (e.g., spatial ability, working memory for visual information). There are as yet no results to report. During this first project year we have begun recruiting androgen-deprivation subjects, but the bulk of the time has been spent in obtaining necessary institutional approvals, which has become a very involved and time-consuming process.				
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ANNUAL REPORT FOR AWARD NUMBER DAMD17-02-1-0040

Cognitive Functioning Among Men with Stage IV Prostate Cancer Undergoing Combined Androgen Deprivation (CAD) Therapy

Introduction

Hormonal treatment of prostate cancer by means of androgen deprivation (AD) can be an effective means of inducing tumor regression and delaying progression of the disease. The treatment, however, adversely affects quality of life (QOL), causing fatigue, depression, impotence, and loss of libido. Anecdotal evidence suggests that cognitive function also may be negatively affected. Because men with prostate cancer may survive for many years if the disease is suppressed, the identification of possible negative influences of life-prolonging treatment on their QOL, and the development of means to treat them, is of great importance. The research questions we are investigating address the relationship between sex steroid levels and different aspects of cognitive functioning. Our specific aims are to: 1) assess whether there is evidence of cognitive impairment among patients on AD therapy; 2) assess the nature and severity of that impairment; 3) determine whether any cognitive deficits observed are related to T suppression, decreased estrogen level, or both; 4) evaluate the relationships between performance on specific cognitive tests and levels of certain sex steroids; and 5) examine the relationship among performance on cognitive measures, steroid levels, and QOL. We are examining men on continuous AD, a matched sample of men on intermittent AD, and a matched sample of healthy controls using tests of working memory, learning, verbal fluency, spatial perception, and verbal reasoning. Each subject is tested at three time points, approximately four months apart. We obtain T and estrogen levels, evaluate cognition, and assess QOL at each timepoint.

Body of Report

As noted in the statement of work (Appendix A), we had anticipated that data collection would begin by the fourth study month. In fact, we only began subject recruitment in the final quarter of calendar year 2002. This delay was a result of requirements imposed by several layers of bureaucracy at the University of Colorado Health Sciences Center (UCHSC) related to human subjects research and to the use of the resources of the University's General Clinical Research Center (GCRC). A chronology of events follows.

We received a memorandum from the Adriene D. King, Ph.D, Human Subjects Protection Specialist with AMDEX Corporation, dated 17 December 2001 requesting minor revisions to the consent form and protocol (Appendix B, page 4). We submitted these revisions to the Colorado Multiple Institutional Review Board (COMIRB) from which we received approval on 11 February 2002 (Protocol Update and Protocol Amendment in Appendix C).

Assuming that we could begin recruitment expeditiously, we submitted a recruitment flyer to COMIRB and received approval from COMIRB on 4 February 2002. This flyer was subsequently distributed at an educational conference, held at the UCHSC, for men with prostate cancer. We received several calls in response from persons interested in serving as research participants, and they were added to a tracking database.

We had planned to use the resources of the GCRC in order to pay for a number of hormone assays. The University's GCRC is funded by the National Institutes of Health to support research studies, covering expenses that otherwise would need to be charged as direct costs to research grants. We learned that because the GCRC is located physically at University of Colorado Hospital, it was therefore necessary to seek the approval of the Hospital Research Resources Committee (HRRC) for the research. We submitted an application to the HRRC on 4 February 2002 (Appendix D), and it was tentatively approved on 27 February 2002, pending approval by the GCRC (Appendix E).

The GCRC meets monthly, and we submitted our application to the Center for review on 1 April 2002. In late April, we received a summary of the comments of the Scientific Advisory Committee (SAC) of the GCRC dated 4 April 2002 (Appendix F). The SAC had a large number of comments which needed to be addressed before approval would be given for the study. A serious illness and subsequent death in my family made it impossible to respond immediately, but on 30 August 2002 I submitted a detailed response to the SAC's critique of the project (Appendix G).

The SAC did not respond until 9 October 2002, at which time they continued to express reservations about the protocol and the assays we were requesting, although they had agreed with all the other points in my response of 30 August (Appendix H). On 14 October 2002, I responded to the SAC (Appendix I), and we received final approval from the GCRC on 31 October 2002 (Appendix J).

On 7 November 2002 we notified the HRRC that we had finally obtained GCRC approval to conduct the study (Appendix K). The HRRC then notified us that all study research personnel having contact with patients would have to go through the Hospital's credentialing process, including purified protein derivative (TB) testing. This was completed, and we received HRRC approval.

A required meeting of the investigators (Grigsby and Glodé) with GCRC clinical and administrative staff was scheduled for mid-December, at which time arrangements were made for use of the GCRC facilities, and lines of communication were established.

We once again began recruiting, and the use of a new flyer and an advertisement letter for eligible patients necessitated COMIRB approval once again. In addition, because the GCRC refused to pay for assays conducted using blood from patients not enrolled at the GCRC, we revised our plans for recruitment to include patients from Western Urologic Research Center, in Wheat Ridge, Colorado. This is a large specialty private practice in the Denver area which has the potential to refer a sizeable number of patients who can be enrolled at the GCRC. However, addition of this site as a source of patients required a protocol update approval by COMIRB. This was first submitted to COMIRB on 8 January 2003 (Appendix L), and they requested additional paperwork on 16 January (which we received on 21 January 2003, Appendix M). We are in the process of submitting an updated protocol amendment (Appendix N), and when approval has been obtained we will in turn submit notification to the Department of Defense IRB.

Finally, on 22 January 2003, we were notified that we must obtain the approval of the University of Colorado Hospital Cancer Center Protocol Review Committee, and we are in the process of preparing that application. Once final approvals are obtained, we already have a preliminary list of eligible subjects. Data collection is ready to begin, and we can start immediately.

Key Research Accomplishments

There are no substantive research accomplishments to report. We have dealt with various regulatory committees, a process that is now nearly complete. Arrangements have been made with the GCRC to begin data collection as soon as all necessary approvals have been obtained. Data collectors have been trained, and both a participant tracking database and a database for entry of participant data have been developed and debugged.

Reportable Outcomes

None to report.

Conclusions

None to report.

APPENDICES TO
ANNUAL REPORT FOR AWARD NUMBER DAMD17-02-1-0040
Cognitive Functioning Among Men with Stage IV Prostate Cancer Undergoing
Combined Androgen Deprivation (CAD) Therapy

APPENDIX A
STATEMENT OF WORK

University of Colorado Health Sciences Center, Denver, CO
Appendices to Annual Report for Award Number DAMD17-02-1-0040
Jim Grigsby, Ph.D., Principal Investigator - January 30, 2003

Statement of Work

- Task 1: Finalize study protocols and preparation for data collection (months 1-3).
- a. Prepare study brochure and consent form describing study for patients (month 1)
 - b. Prepare written protocols for recruitment, data collection, and data management (months 1-2)
 - c. Recruit and train data collectors (months 1-3)
 - d. Prepare data collection instruments (months 1-2)
 - e. Prepare database (months 1-3)
- Task 2: Conduct of study (months 3-30).
- a. Begin subject recruitment and data collection (month 3)
 - b. Begin first follow-up data collection [time point 2] (month 6)
 - c. Subject recruitment completed (month 26)
 - d. Time point 3 follow-up data collection completed (month 32)
- Task 3: Interim data analysis (months 24-30).
- a. Preliminary data edits and transformations (months 24-27)
 - b. Preliminary descriptive analyses (months 27-30)
- Task 4: Annual reports.
- a. Prepare annual report for year 01 (months 11-12)
 - b. Prepare annual report for year 02 (months 23-24)
- Task 5: Final data analysis and report preparation (months 28-36).
- a. Specification of final data analyses (months 28-31)
 - b. Conduct final data analyses (months 32-34)
 - c. Write articles and submit for publication (months 28-36)
 - d. Write final report (months 34-36)

APPENDIX B

MEMORANDUM FOR RECORD

This appendix contains a December 17, 2001 memorandum from Adriene D. King, Ph.D., Human Subjects Protection Specialist with AMDEX Corporation requesting minor revisions to the consent form and study protocol.

A-11079 Grigsby

MCMR-RCQ (70-1n)

17 December 2001

MEMORANDUM FOR RECORD

SUBJECT: Protocol Entitled "Cognitive Functioning Among Men with Stage IV Prostate Cancer Undergoing Combined Androgen Deprivation (CAD) Therapy," Submitted by Jim Grigsby, Ph.D., University of Colorado Health Sciences Center, HSRRB Log No. A-11079, Proposal No. PC010257, Award No. DAMD17-02-1-0040.

1. Background. The protocol was awarded as a New Investigator Award under the DoD Prostate Cancer Research Program.
2. Scientific Review. The protocol received scientific peer review by a clinical health services panel to USAMRMC on 20-22 May 2001.
3. Review by IRB of Record. The Colorado Multiple IRB (COMIRB) reviewed and approved this study by expedited review on 26 July 2001. Continuing review is due 25 July 2002.
4. Level of Risk Assessment. This study is minimal risk because it will involve the collection of blood by standard venipuncture and it will require the completion of standard questionnaires to assess cognition. Measures are in place to maintain confidentiality. In addition, this study does not involve treatment.
5. Research Design. This is a prospective cohort study involving prostate cancer patients and healthy men as controls. This study will not involve intervention rather it seeks to assess the quality of life of men on an androgen deprivation protocol for treatment of Stage IV prostate cancer. The study will involve the collection of blood samples, the completion of mood and quality of life instruments and an assessment of the influence of androgens on cognition. Patients on intermittent CAD or continuous CAD will be given cognitive tests three times during the course of this 36 month study, which means at baseline and every 12-16 weeks. Blood will also be drawn at these time points to determine serum testosterone levels and other sex hormones.
6. Research Objectives. There are several aims to this study, as mentioned on page 3 of the protocol. They are as follows:
 - a. To assess whether there is evidence of cognitive impairment among patients on combined androgen deprivation (CAD) therapy.
 - b. To assess the nature and severity of that impairment, evaluating different aspects of cognition.
 - c. To use cognitive tests sensitive to fluctuations in levels of testosterone or estrogen, and others that are unaffected by plasma sex steroid level, to evaluate whether deficits observed are related directly to changes in the level of testosterone, the level of estradiol or of both.

Processing, Declarative Verbal Learning and Memory, Verbal Reasoning, Verbal Fluency, Spatial Perception, Depression, and Quality of Life and Fatigue. Each of these is described in detail on pages 6-7. Data collectors at each center will be responsible for enrolling subjects and administering all study instruments. The instruments for cognitive assessments will be administered at baseline and every 12-16 weeks thereafter, for a total of three timepoints. At each timepoint, blood will also be collected to perform assays to determine serum levels of testosterone and other sex hormones (refer to page 8).

12. Data Analysis Plan. As mentioned on page 8 of the protocol, data management and analysis will be conducted at the Center for Health Services Research and data will be double-entered for quality control. SPSS and SAS will be used for analysis. To characterize samples within each group, frequency distributions and descriptive statistics will be used. ANCOVA and MANCOVA will be used for continuous measures of cognition. For dichotomous measures, logistic regression models will be applied and multiple regression will be used to assess the contribution of a number of different variables to specific dependent variables.

13. Risks to Subjects.

Procedure	Risks	Measures to Minimize Risks
Venipuncture	Discomfort, bruising, pain	Not described
Completion of questionnaires	Fatigue, anxiety, psychological and emotional responses/risk	-Data collectors will monitor subjects closely to ensure that no physical harm comes to the subjects while performing the tasks. -To avoid fatigue, subjects will be given a break between tasks involved with the assessments. -No sensitive information will be obtained that would elicit a harmful psychological or emotional response.
Study participation	Breach of confidentiality	-Each participant will be assigned a numerical code. -Identifying info will be kept separate from all study data. -All records will be kept in locked cabinets. -Computerized databases will be password-protected. -After data collection is completed for a subject, identifying data fields will be deleted for that subject. -Data will only be presented in aggregate form. -Only authorized study personnel will have access to subject data.

14. Benefits to Subjects. There are no anticipated benefits to subjects who participate in this study.

15. Recommendations for Approval.

- a. Revisions to be made to the protocol.

APPENDIX C

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD (COMIRB) PROTOCOL AMENDMENT AND PROTOCOL UPDATE APPROVAL FORMS

This appendix contains the Colorado Multiple Institutional Review Board (COMIRB) approval forms in response to protocol and consent form changes made at the request of the Department of Defense (see 12/17/01 memorandum contained in Appendix B). These forms include an Alterations and Update(s) Form and a Protocol Amendment(s) Form, both of which were approved on February 11, 2002.



Colorado Multiple Institutional Review Board
13001 E. 17th Place
Building 500, Room N3214
Aurora, Colorado 80010-7238

Mailing Address:
Mail Stop F-490
P.O. Box 6508
Aurora, Colorado 80045-6508

(303) 724-1055 [Phone]
(303) 724-0990 [Fax]
comirbweb.uchsc.edu [Web]
comirb@uchsc.edu [E-Mail]
Assurance # M-1494-01

University of Colorado Hospital
Denver Health Medical Center
Veteran's Administration Medical Center
The Children's Hospital
University of Colorado Health Sciences Center
Colorado Prevention Center

DEVORE, PATRICIA
Campus Box C241

02/12/2002

Certificate of Approval

Investigator: JIM GRIGSBY

Sponsor: DEPARTMENT OF DEFENSE

Subject: **COMIRB Protocol 01-522
Amendment Review (PAM001)
1st Review**

Title:

EFFECTS OF ANDROGEN BLOCKADE ON COGNITIVE FUNCTION AND
QUALITY OF LIFE IN MEN WITH PROSTATE CANCER

Approval Date: **11 February 2002**

Approval Includes:

Protocol Amendment Approved

Dated: 1 February 2002

Description: Changes to the protocol requested by the Dept. of Defense include-

- State videotapes by destroyed after study completion
- Describe the number of data collectors along with their qualifications
- Describe the interrater reliability procedure
- Add section "Modification of the Protocol indicating any changes to protocol to be approved by COMIRB and the HSRRB of the Dept. of Defense
- Add new section describing the roles and responsibilities of study personnel
- Add HSRRB Clause 1.02 Reporting of Serious Adverse Events

Attachments:

Memorandum from the Dept. of Defense
Revised highlighted Study Protocol

Christopher Kuni, MD Chair
Ken Easterday, RPh Co-Chair

Stephen Bartlett, RPh Chair
Norman H. Stoller, DMD Co-Chair

Adam Rosenberg, MD Chair
Dave Lawellin, PhD Co-Chair



Colorado Multiple Institutional Review Board
 13001 E. 17th Place
 Building 500, Room N3214
 Aurora, Colorado 80010-7238

Mailing Address:
 Mail Stop F-490
 P.O. Box 6508
 Aurora, Colorado 80045-6508

(303) 724-1055 [Phone]
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 comirbweb.uchsc.edu [Web]
 comirb@uchsc.edu [E-Mail]
 Assurance # M-1494-01

University of Colorado Hospital
 Denver Health Medical Center
 Veteran's Administration Medical Center
 The Children's Hospital
 University of Colorado Health Sciences Center
 Colorado Prevention Center

DEVORE, PATRICIA
 Campus Box C241

02/12/2002

Certificate of Approval

Investigator: JIM GRIGSBY
 Sponsor: DEPARTMENT OF DEFENSE
 Subject: **COMIRB Protocol 01-522
 Update Review (UPD002)
 1st Review**

Title:
 EFFECTS OF ANDROGEN BLOCKADE ON COGNITIVE FUNCTION AND
 QUALITY OF LIFE IN MEN WITH PROSTATE CANCER

Approval Date: **11 February 2002**

Approval Includes:

Protocol Update Approved

Dated: 1 February 2002

Description: Consent Form Revision:
 1. New section entitled "Alternative Procedures Available to Subjects"
 2. Clarify the procedures taken to minimize the risks associated with venipuncture and with the questionnaire completion.
 3. Add contact information in the event of a research-related injury.
 4. Change amount of blood drawn from 15 ml to 20 ml for each of the separate blood draws.
 Attachments:
 Revised Highlighted Consent Form

Christopher Kuni, MD Chair
 Ken Easterday, RPh Co-Chair

Stephen Bartlett, RPh Chair
 Norman H. Stoller, DMD Co-Chair

Adam Rosenberg, MD Chair
 Dave Lawellin, PhD Co-Chair

APPENDIX D

HOSPITAL RESEARCH RESOURCES COMMITTEE (HRRC) APPLICATION

This appendix contains the HRRC Approval Form from the application submitted to the Hospital Research Resources Committee (HRRC). Because the University's General Clinical Research Center (GCRC) is located physically at the University of Colorado Hospital, it is necessary to seek the approval of HRRC for the research.



University of Colorado Health Sciences Center

Center for Health Services Research

1355 So. Colorado Blvd., Suite 306
Denver, Colorado 80222
(303) 756-8350
FAX: (303) 759-8196

February 4, 2002

Ms. Mary Schumer
Research Administrator
University of Colorado Hospital
Campus Box A021-810
4200 East 9th Avenue
Denver, CO 80262

Dear Ms. Schumer:

Enclosed, you will find application materials for HRRC review of a study entitled "Effects of Androgen Blockade on Cognitive Function and Quality of Life in Men with Prostate Cancer" (COMIRB protocol number 01-522). Included with this letter are ten packets containing copies of the following documents:

- I. HRRC Approval Form (Including HRRC Budget Form)
- II. HRRC Research Personnel Credentials Review Form
 - A. Angela Brega
 - B. Patricia DeVore
 - C. Jim Grigsby
- III. COMIRB Application Form
- IV. COMIRB Approval Letter
- V. Protocol Summary
- VI. Subject Consent Form

In addition to these materials, one copy each of the Master Protocol and the current Project Budget are enclosed.

If you have any questions or need further clarification of the study protocol, please feel free to call me at the number listed above. Thank you for your consideration.

Sincerely,

Angela Brega, PhD
Co-Investigator



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HRRC APPROVAL FORM FOR CONDUCTING RESEARCH

Primary Information

COMIRB # 01-522 UCHSC Grants & Contracts # 2-5-50034

Protocol Title: Effects of Androgen Blockade on Cognitive Function and Quality of Life in Men with Prostate Cancer
 Study Sponsor: Department of Defense UCH Billing Contact: NA
 Principal Investigator (Print): Jim Grigsby, PhD Phone: (303) 756 8350 Fax: (303) 759 8196
 Principal Investigator's Department: Medicine (Geriatrics) Campus Box: C-241
 Rm.# Center for Health Services Research, 1355 South Colorado Blvd., Denver, CO 80222, Ste. C-306
 Research Coordinator (Print): Patricia DeVore Phone: (303) 756 8350 Campus Box: C-241
 Please list any additional non-physician personnel who will be providing direct patient care:
 Name(s): NA - No direct patient care will be provided.
 Co-Investigator(s): Angela Brega, PhD, Mike Glodé, MD, Wendolyn Gozansky, MD, and Peter Shaughnessy, PhD

Study and Participant Information

When is this study expected to begin? 2/1/2002
 When is the renewal/termination date for this protocol? Study end date is January 6, 2005
 Will investigational devices be utilized during the study? No
 If Yes, how is the device categorized by the FDA? Select "A" or "B"
 How long will each participant be a part of the study? 18 months (5 hours total)
 Will monetary compensation be offered to participants? No Yes
 If Yes, specify amount and process:
 Will this study involve use of the Adult General Clinical Research Center (GCRC)? No Yes
 Will this study involve use of the Pediatric General Clinical Research Center (GCRC)? No Yes

Projected Volume: Anticipated patient volume for duration of study

Inpatient: Projected total number of inpatient participants? 0
 Projected total number of inpatient admissions? 0
 Will the study increase the length of stay for inpatient admissions? No Yes

Outpatient: Projected total number of outpatient participants? 50
 Projected total number of outpatient visits? 150 (3 visits per participant)



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HRRC APPROVAL FORM FOR CONDUCTING RESEARCH

Ancillary Services: This section MUST be completed if the services below will be utilized.

Pharmacy: For pharmacy questions, please contact the Investigative Drug Service Pharmacist at (303) 372-6625.
 Will investigational medications be used? No Yes
 Will the UH Pharmacy be required to mix or dispense medications? No Yes
Pharmacy contact's name (Print): _____
Pharmacy contact's signature of agreement: _____ **Date:** _____

Laboratory: For laboratory questions, please contact the Client Services Manager at (303) 372-0320.
 Will the UH Laboratory be required to process lab work? No Yes
 Will special lab procedures be necessary? No Yes
Laboratory contact's name (Print): GCRC will conduct and pay for all lab work.
Laboratory contact's signature of agreement: _____ **Date:** _____

Radiology: For imaging/radiology questions, please contact the UH Director of Radiology at (303) 372-0220.
 Will UH Imaging/Radiology services be required? No Yes
Radiology contact's name (Print): _____
Radiology contact's signature of agreement: _____ **Date:** _____

Direct Patient Care Services: This section MUST be completed if research involves direct patient care. The UCH Approval Form WILL NOT BE PROCESSED without the appropriate signatures below.

Inpatient Services: For inpatient service questions, please contact the Director/Manager of the clinical area.
 Will special nursing services be required beyond standard-of-care and usual staffing patterns? No Yes
 If "yes", please explain:
Please note: All direct care clinical research REQUIRES staff education.
 Is there a plan for staff education? No Yes Not Applicable – No direct patient care will be provided.
 If appropriate, briefly explain the plan for staff education:
Manager/Director's name (Print): _____
Manager/Director's signature of agreement: _____ **Date:** _____

Outpatient Services: For ambulatory service questions, please contact the Practice Manager.
 Will the study impact outpatient scheduling services? No Yes
Please note: All direct care clinical research REQUIRES staff education.
 Is there a plan for staff education? No Yes Not Applicable – No direct patient care will be provided.
 If appropriate, briefly explain the plan for staff education:
 Is the budget amenable to outpatient care provisions? No Yes
Practice Manager's name (Print): _____
Practice Manger's signature of agreement: _____ **Date:** _____



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HRRC APPROVAL FORM FOR CONDUCTING RESEARCH

Use of Hazardous Material

Will this study use Gene or Recombinant DNA Therapy? No Yes
 If "yes", the following is required:
 UCH Safety Officer Signature
 UCHSC Biohazards Form (Form 86-1)
 UCHSC Registration Form for the use of biological materials (Form 101)
 UCH Safety Officer's name (Print): _____
 UCH Safety Officer's signature of agreement: _____ Date: _____

ATTACHMENTS

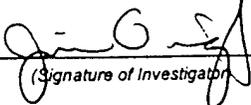
Please include the documents noted below. Failure to do so WILL delay HRRC Approval.
 Send to: Mary Schumer, Research Administrator
 Campus Box A021-810

(1). *Ten collated copies of:*
 a. HRRC Approval Form
 b. COMIRB Application
 c. COMIRB Approval Letter (if available)
 d. Protocol Summary
 e. Subject Consent

(3). One copy of the Master Protocol
 (4). One copy of the Clinical Trial Agreement & Budget

Signature of Investigator

(Please Note: Applications without the Investigator's signature WILL NOT BE PROCESSED).

I, , do hereby certify that all information contained herein this HRRC Application for Approval is truthful and accurate.

Signed this day, 1-25-02
 (Date)

UCH APPROVAL

HRRC CHAIRPERSON APPROVAL: _____
 (Signature) (Date)

Please Note: Page 4 is the "Budget Worksheet"

APPENDIX E

APPROVAL FROM HOSPITAL RESEARCH RESOURCES COMMITTEE (HRRC)

This appendix contains an e-mail noting tentative approval by the Hospital Research Resources Committee (HRRC) on February 27, 2002 pending approval from the University's General Clinical Research Center (GCRC).

Brega Angela

From: Schumer Mary
Sent: Wednesday, February 27, 2002 10:51 AM
To: Grigsby Jim; Brega Angela
Subject: 01-522, Androgen Blockade on Cognitive Function

Drs. Grigsby and Brega:

The above study will be approved by the HRRC pending the following:

1. Confirmation of GCRC approval with the services covered defined
2. Clarification of the site of study participant's visits? Will the study participants be seen in the clinic or on the GCRC?

Thanks,

Mary Schumer, MS, CPA
Research Administration
University of Colorado Hospital
Phone: 303-372-4067
FAX: 303-372-4064
e-mail: mary.schumer@uhcolorado.edu

APPENDIX F

COMMENTS FROM THE SCIENTIFIC ADVISORY COMMITTEE (SAC) OF THE UNIVERSITY'S GENERAL CLINICAL RESEARCH CENTER (GCRC)

This appendix contains the April 4, 2002 comments from the Scientific Advisory Committee (SAC) of the University's General Clinical Research Center (GCRC). The SAC would not approve the study until these comments were addressed.



General Clinical Research Center - Adult

Campus Box B141
4200 East Ninth Avenue
Denver, Colorado 80262
(303) 372-8799
(303) 372-8819 FAX

April 4, 2002

James Grigsby, Ph.D.
Box C241

Re: Protocol 1308: Effects of Androgen Blockade on Cognitive Function and Quality of Life in Men with Prostate Cancer

Dear Dr. Grigsby:

Thank you for submission of your protocol, which was reviewed by the Scientific Advisory Committee on 1 April 2002. The committee felt that this was an interesting proposal, but did voice several concerns. We are, therefore, requesting a revised protocol with a cover letter detailing your responses. This will then need to be reviewed by the statistician, the primary reviewers, and the chairman before a final determination can be made.

1. The first concern was that the committee did not have the entire SWOG protocol to review. Therefore, we did not know whether you are near the end, in the middle, or early in your recruitment phase. This could severely impact the type of data you can obtain from this protocol, and therefore, in your revision, please attach the full SWOG protocol.
2. Related to the above concern was whether you would be able to obtain baseline measurements in patients prior to androgen deprivation therapy. Since there is potential for numerous covariates to exist between the three populations (controls, those treated with continuous treatment versus intermittent), it may be difficult to interpret any differences in your cognitive testing. However, if baseline measurements could be obtained in these patients that would greatly strengthen your design. Therefore, please provide us with some information on how many patients studied will have a baseline and then post-treatment measurements.
3. Please provide us with further information regarding the exact kind of androgen deprivation therapy that is going to be provided in this protocol. Here again, reviewing the entire protocol would be helpful. However, we would like to know the specific therapies that will be given to these patients.
4. No justification was provided for the salivary cortisol levels. Therefore, this part of the protocol has been denied.
5. Please provide further justification for the measurement of estrone. This assay is not well standardized and little normative data are available. How would this add to the more conventional measurement of estradiol?

James Grigsby, Ph.D.
April 4, 2002
Page 2

6. Adrenal androgens are not discussed, but should be measured. In particular, one reviewer suggested measuring DHEA sulfate rather than DHEA. The former is nonpulsatile and is only made by the adrenal, whereas the latter is pulsatile and can be made by the adrenal gonads and fat.
7. Please add measures of overall disease severity. Thus, these patients could vary from fairly active to near terminal.
8. A huge battery of cognitive tests were proposed. Please comment on whether patients can complete this battery and not succumb to fatigue.
9. Please elucidate a primary endpoint for the cognitive studies. This is critical to be able to interpret your data. As written, given the numerous domains of measures from this battery of tests, you are at great risk of having Type 1 errors.
10. Please see the attached statistical review. Also, our statistician is requesting a discussion with you regarding this protocol.
11. Several administrative issues were identified. The consent form is incomplete because it did not fully discuss alternative treatment or compensation for injury. Also, please note that the GCRC will not be able to provide additional nursing support for the cognitive testing requested.
12. Please note that the collaborating GCRCs will be responsible for covering the cost of the total testosterone and albumin levels. Also, please note that the GCRC core lab will perform the DHEA samples.
13. Please ensure that the title on the consent form and the GCRC protocol match.
14. Please include some information under the Progress Report and Preliminary Studies section per the instructions on the GCRC website.
15. The timing of the testing should ensure that it occurs at the maximal effectiveness of the GnRH agonists in suppressing gonadal steroid levels and not the last days before the next injection.

In summary, the committee had a number of concerns with this protocol, but we do feel after substantial revision and discussion with the statistician that this could be an approved protocol.

Sincerely,

William R. Hiatt

William R. Hiatt, M.D.
Professor of Medicine
Chairman, Scientific Advisory Committee

John Routes

John Routes, M.D.
Associate Professor of Medicine
Co-Chair, Scientific Advisory Committee

Cc: John Kittelson

1. Repeated measures ANOVA or ANCOVA should be fit using modern methods for mixed models.
2. Analysis plan proposes use of MANOVA for the multivariate outcomes associated with cognitive tests. The motivation for this approach appears to be controlling the type I error rate. The analysis plan also expresses concern over multiple comparisons problems and suggests the Holm method to avoid inflation of the type I error rate. I have two comments on this approach:
 - a. Over-correction for multiple comparisons results in loss of power. Many of the hypotheses in the proposal are exploratory in nature, and I would worry more about the type II error than controlling the type I error.
 - b. Use of MANOVA (or MANCOVA) is another form of protection for inflated type I errors. The problem is that it can obscure the scientific interpretation. I wonder if it is not better to develop meaningful scales (as in likert scores) so that scientific interpretability is maintained. The problem with multivariate statistical methods is that they have nice theory for testing, but do not provide good estimates; thus, you can decide if the null hypothesis can be rejected, but you cannot interpret what it means if it is.
3. The sample size justification is based on effect sizes. This is a symptom of working with analysis approaches like MANOVA. Once again, the result is the loss of scientific interpretability. As an alternative I advocate for prioritization of outcomes and designing the study to detect important differences in the scale of the most important outcome. There is no such thing as a universal rating of effect sizes as small, medium, or large (*ala* Cohen, 1977). The magnitude of what is important is context-specific (as well as instrument-specific); for example, the definition of a clinically important change in cognitive function is likely to be different in different types of subjects.

Other questions/comments:

1. There is potential for systematic differences between prostate cancer patients and healthy males that may well affect cognition by pathways that are unrelated to androgen hormonal levels. How will this be addressed? What other demographic or baseline status data will be collected to adjust for the potential confounding?
2. Adjusting for testosterone levels in the models will potentially remove any differences between the three groups. The first hypothesis seems to require an unadjusted analysis.
3. The statistical models necessary to answer these questions should be fit by someone who is familiar with their vagaries. I recommend that the investigators contact a biostatistician for assistance with the analysis.

APPENDIX G

RESPONSE TO THE SCIENTIFIC ADVISORY COMMITTEE (SAC) OF THE UNIVERSITY'S GENERAL CLINICAL RESEARCH CENTER (GCRC)

This appendix contains the August 30, 2002 detailed response to the critique of the project by the Scientific Advisory Committee (SAC) of the University's General Clinical Research Center (GCRC) (see 04/04/02 SAC comments in Appendix F).



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30 August 2002

William R. Hiatt, MD
Chairman, Scientific Advisory Committee
General Clinical Research Center

Re: Protocol 1308, *Effects of androgen blockade on cognitive function and quality of life in men with prostate cancer*

Dear Dr. Hiatt:

This is in response to your letter of April 4, 2002, regarding the above protocol. I apologize for the delayed response, but circumstances made a more timely reply impossible. In this letter I will respond to each of the Scientific Advisory Committee's comments by number. I also have met with John Kittelson, and discussed the data analysis with him.

1. The committee requested the entire SWOG protocol for review. Since the SWOG protocol might be characterized as voluminous, we had not submitted it with the original protocol. Moreover, our own protocol is independent of the SWOG protocol, to which it is a very small supplement, and it was my assumption that our description of the proposed study was adequate. However, as requested, we have attached the full oncology consortium protocol and its addenda for the reading enjoyment of the Committee. The Committee's concern was apparently that too few subjects might be available for recruitment. This concern is unwarranted. As of early this month, 1396 patients had been recruited toward an accrual goal of 3,024. Of those individuals recruited, 703 had been randomized. Hence the current stage of the treatment protocol should have a negligible effect on our capacity to obtain data on 80 subjects undergoing androgen deprivation therapy.
2. The Committee expressed concern regarding the availability of baseline measurements of subjects' cognitive functioning. We proposed to study three groups: 1) those on the continuous androgen deprivation regimen, 2) those on intermittent blockade, and 3) controls. We proposed recruiting 40 subjects for each group. *Baseline* in this study is defined as that physiologic state in which a subject has what is, for him, a "normal" level of testosterone. For those individuals in the intermittent protocol, we will have baseline data on all subjects since they will be examined first prior to initiation of treatment (OFF). They then will be examined when prostate specific antigen (PSA) (and testosterone [T]) have been stabilized at undetectable levels for several weeks (ON), and again approximately 3-4 months after treatment has been suspended and T production has returned to baseline (OFF). For those individuals in the continuous protocol, we will attempt to examine all subjects prior to initiation of treatment (OFF), then twice subsequently while undergoing androgen blockade (ON). We will make every effort to recruit the continuous protocol patients prior to initiation of therapy, but we anticipate that as many as 10%-15% may have already begun treatment. We propose to deal with this, should it occur, in the data analysis phase of the project. One approach would be to create dummy variables for ON/OFF treatment and use these in regression models. We also will have T levels (and levels of several other steroids), which could themselves be entered in the analysis. We will compare the slopes across the three timepoints for all three groups, and for individuals in the continuous group who either are, or are not, androgen deprived at initial data collection session. It should be kept in mind that the fundamental distinction between ON and OFF conditions is that T is fully suppressed (ON), or it is at

an individual's typical level (OFF) given variability within the general population within the age range to be studied (primarily older).

3. The Committee requested specific information about the androgen deprivation therapies to be provided as part of this protocol. To clarify, the project we are proposing involves no treatment of or intervention with patients. The current protocol simply takes advantage of an ongoing multi-site treatment study in order to examine a specific aspect of the quality of life of a subset of individuals participating in that research. In the SWOG study, following an initial induction phase involving eight courses (seven months) of CAD therapy, stage IV prostate cancer patients are randomized to one of two arms. Patients assigned to the first arm receive continuous CAD, even in the absence of disease progression (as determined by level of PSA). Individuals assigned to the second arm, following the induction phase, discontinue CAD therapy and are observed until either their PSA levels rise to approximately 20 ng/mL or they show clinical signs of disease activity. At that time, patients resume CAD for a second round of eight courses (seven months), after which time, if PSA is within normal limits, CAD is again discontinued. The agents to be used include bicalutamide (Casodex™), which is a non-steroidal antiandrogen with no androgenic or progestational properties, and goserelin acetate (Zoladex™), which is a luteinizing hormone releasing hormone analogue. For more details on these agents, please refer to the SWOG protocol.
4. Your letter stated that “no justification was provided for the salivary cortisol levels. Therefore, this part of the protocol has been denied.” We want to appeal this decision. Salivary cortisol levels are highly correlated with serum cortisol (e.g., Cook, 2002; Gallagher et al., 2002; Gröschl et al., 2001, 2002; Kahn et al., 1988; Kirschbaum & Hellhammer, 1989, 1993; Kirschbaum et al., 1992). The primary advantage of using salivary cortisol rather than serum cortisol is that it is noninvasive, and can more easily be collected twice (morning and evening) than is the case for blood draws, decreasing the burden on participants. Salivary cortisol is widely used, and assays using saliva samples have been used to study a wide range of cognitive and psychological/psychiatric outcomes (e.g., Bohnen et al., 1992; Cho et al., 2001; Kozora et al., 2001; Lupie et al., 2001; Monk & Nelson, 2002; Neyla et al., 2001; Scarpa & Luscher, 2002; van Niekerk et al., 2001; Vedhara et al., 2000; Young et al., 2002). Both level of cortisol and diurnal variability have been associated with various aspects of cognition, and may be important as covariates in this study of steroids and cognition, in which the normal hormonal milieu is altered markedly by androgen suppression.
5. The Committee requested “further justification for the measurement of estrone,” noting that “this assay is not well standardized and little normative data are available.” We request that total estrogens, estrone (E1) as well as estradiol (E2), be assessed in our subjects to determine whether changes in estrogen levels, independent of changes in androgen levels, affect cognitive performance. Healthy men secrete a small amount of E1 from the testes (6 ug/d) with the majority of E1 (66ug/d) and E2 (45 ug/d) produced from peripheral aromatization of androgens (Williams Textbook of Endocrinology, p 827). Because E1 can be converted locally to the more active E2 in several tissues, including brain (C Martel. *J Steroid Biochem Mol Biol* 1992;41:597-603), we believe assessment of both circulating estrogens may provide a more accurate measure of estrogen exposure at the tissue-level. However, sex hormone binding globulin (SHBG) will be used to calculate the “free” hormone levels because bioavailable estrogens, which decline with age in healthy men, independently predict other estrogen-dependent physiologic outcomes such as bone mineral density (S. Khosla *JCEM* 1998; 83:2266-2274; S Khosla *JCEM* 2001; 86:3555-3561). Endogenous E1 and E2 levels have shown divergent associations with cognitive function and mood (K Yaffe. *J Am Geriatr Soc.* 1998 Jul;46:918-920; B Breuer. *Am J Geriatr Psychiatry* 2002;10:311-320; E Barrett-Connor *J Clin Endocrinol Metab* 1999;84:3681-3685; and others), suggesting that comprehensive assessment of the sex hormone milieu may be important for interpretation of the findings. Furthermore, GnRH agonist therapy has been shown to decrease both E1 and E2 as well as decreasing androgen production (LM Eri, *Scand J Clin Lab Invest* 1996;56:319-325). Therefore, documentation of changes in total bioavailable estrogens as well as androgens may help

explain changes in cognitive function for men undergoing androgen deprivation therapy for prostate cancer. Standardization and normative data are not relevant in this case since we are making within- and between-groups comparisons, and are not concerned with where the values lie with reference to norms.

6. The Committee suggested that DHEA sulfate be measured rather than DHEA. We agree, and acknowledge this oversight in our original proposal. We therefore request DHEAS assays.
7. Although it may not have been mentioned in our GCRC protocol, disease severity will be measured using the Eastern Cooperative Oncology Group (ECOG) Performance Status measure (Oken et al., *Am J Clin Oncol*, 1982;5:649-655). A copy is attached.
8. The Committee observed that "a huge battery of cognitive tests were proposed. Please comment on whether patients can complete this battery and not succumb to fatigue." In fact, the battery requires relatively little time. We estimate that, at most, the 10 cognitive instruments will require 90 minutes for completion. We have used considerably more extensive cognitive batteries with a number of elderly and ill populations, and have noticed no problems with subjects succumbing to fatigue. However, as noted on pages 5 and 6 of our original protocol, in order "to minimize fatigue, there will be a break midway through administration and more frequently if needed. For those unable to complete the testing in one sitting, they will be tested over two sessions. Data collectors will be trained to evaluate fatigue and asked to reschedule testing if fatigue appears to affect performance."
9. I have addressed the problem of Type I error with Dr. Kittelson, and believe this presents minimal problems. We hypothesize that the most significant problems will be in the areas of working memory, and the capacity and speed of information processing. One measure (the Similarities subtest of the Wechsler Adult Intelligence Scale) is to be used as a covariate proxy for verbal intelligence. The primary endpoints are the Letter-Number Sequencing test (working memory), Grammatical Reasoning (information processing), Logical Memory subtest of the Wechsler Memory Scale (verbal learning), and the Vandenberg and Kuse Mental Rotations Test (spatial perception). Our interest in the other cognitive measures is largely to determine whether they confirm results on these measures. In addition, it should be noted that we proposed to use the Holm method of adjusting for multiple comparisons. This, and our prior suggested use of multivariate analyses, would obviate the Committee's worry that we would be "at great risk of having Type I errors." I discussed the Committee's concern with Dr. Kittelson, who suggested that even the adoption of a somewhat less conservative alpha level than might be indicated by Holm's approach (e.g., $\alpha = 0.01$) would be acceptable. In addition, we now intend to use an approach other than the multivariate one, as will be discussed below.
10. Dr. Kittelson suggested some modifications in the analytic approach we previously proposed. We will follow his advice, and also will request consultation with a GCRC statistician in the specification and interpretation of analyses for this project. Instead of using multivariate analyses of variance and covariance, we have developed a hierarchy of outcomes, with four major and several secondary outcomes (as noted above in my response to point 10). In order to avoid Type I error, we originally proposed using the Holm method (which is analogous to that of Bonferroni), but Dr. Kittelson suggested that the adoption of a conservative alpha (0.01) would be sufficient. In lieu of multivariate analyses, we will compare the slopes and intercepts for subjects within each of the three groups across the three timepoints. We will use random effects mixed models for inferential analyses, and are especially interested in interaction terms between group membership and dependent variables, as well as elapsed time and outcomes. Our major steroid variable is total T, but we are interested as well in the interaction between T and other endocrine measures. With respect to power calculations and sample size estimates, Dr. Kittelson had noted in his comments our reference to Cohen (1977) and effect sizes. We made this reference only to characterize the size of the effects we anticipated. Our estimates in fact were derived from literature on differences in cognitive functioning associated with variable estrogen levels among women (e.g., Hampson, 1990; Hampson & Kimura, 1988), and from our estimates of

what would be a clinically meaningful change in cognition. For the various measures, these effect sizes range from about 0.3 to 1.5, and hence we assumed an effect size of 0.4, which is approximately what Cohen would characterize as small to medium.

11. The Committee argued that the “consent form is incomplete because it did not fully discuss alternative treatment or compensation for injury.” I will note that the consent form was approved by both COMIRB as well as the Department of Defense Human Subjects Research Committee. There was no discussion of alternative treatments because there is no treatment involved in this protocol. The alternative is not to participate in this study of the effects on cognition of androgen suppression. Under the section titled “Alternative Procedures Available to Subjects,” it was stated that “there is no alternative procedure available to subjects who participate in this study. You are, however, free to decline to participate in this study if you wish.” Because this is not a treatment study, and because any risks are of an extremely low order of probability and of doubtful significance, neither COMIRB nor the DoD thought it necessary to discuss compensation for injury. Finally, please note that we are not requesting any “additional nursing support for the cognitive testing required,” and no mention was made of any such request in the protocol. Given previous multiple IRB approvals, we contend that the existing consent form should be adequate. Should the Committee insist on changes in the consent, this will require sequential resubmission of the consent form to both COMIRB and the DoD human subjects review boards.
12. Your letter stated that “the collaborating GCRCs will be responsible for covering the cost of the total testosterone and albumin levels.” There are no collaborating GCRCs for this project, which is distinct from the SWOG protocol. While we anticipate that we will collect some data from patients enrolled in the SWOG protocol at sites other than UCHSC (oncologists at University of Washington and Wayne State University are likely participants), the budget only contains funding to cover the time of data collectors in obtaining and transmitting the cognitive and related data, and drawing blood. No other participating sites will receive any indirect costs from this grant. We request that the assays be done at UCHSC, as otherwise it will not be possible to involve multiple data collection sites.
13. The title on the consent form and the GCRC protocol now match, that on the GCRC protocol having been revised.
14. Your letter asked that we “include some information under the Progress Report and Preliminary Studies section per the instructions on the GCRC website.” According to the website, “If this is a continuing study provide a progress report. If this is a new study, describe any work that you have done in this area that has prepared you to carry out the proposed study. Include pilot studies or prior studies by the principal investigator that have laid the foundation for the proposed research study.” This is not a continuing study, so there is no progress report to provide. Moreover, no previous work has been done by the Principal Investigator in the area of cognitive functioning and sex steroids. The PI has, however, conducted research involving the cognitive assessment of a number of clinical and normal populations, including normal and demented elderly, normal younger adults, persons with multiple sclerosis, CVA patients, persons with the fragile X full mutation and premutation, persons who inhale organic solvents, persons in chronic pain, individuals who have sustained head traumas ranging from mild through severe, and individuals with complex partial seizures. These studies involved cognitive batteries of differing complexity, and as the results of those studies are too detailed to discuss here (and not directly relevant to the issue of testosterone and cognition), a partial bibliography has been appended to this letter. I also have included selected references to the work of Sanjay Asthana, MD, a consultant at the University of Wisconsin who has conducted a number of studies of estrogens and cognition. Finally, although she is not formally a co-investigator, Wendee Gozansky, MD, of UCHSC, is affiliated with the research team. Dr. Gozansky has conducted research on endocrine functioning among the elderly.
15. Your letter noted that “the timing of the testing should ensure that it occurs at the maximal effectiveness of the GnRH agonists in suppressing gonadal steroid levels and not the last days before

the next injection.” Dr. Glodé maintains that this is not an issue given the nature of the treatment provided under the SWOG protocol. Goserelin is a depot preparation administered subcutaneously every 28 days. Bicalutamide tablets are taken orally once daily. T remains suppressed, in most cases, for several weeks after the last administration of the drugs. As noted in our protocol, “patients on intermittent CAD will be administered cognitive tests: 1) at baseline (before beginning AD) if possible, or 12-16 weeks after discontinuation of androgen blockade; 2) 12-16 weeks following resumption of androgen blockade; and 3) 12-16 weeks after discontinuation of androgen blockade. Patients on continuous CAD also will be examined at three time points: 1) at baseline (before AD) if possible or after at least 12 weeks on AD; 2) after another 12-16 weeks of continuous AD; and 3) after another 12-16 weeks of AD. This design will allow comparison of the effect of CAD on cognition while controlling for practice effects. Control subjects also will be administered the tests on three occasions: 1) at baseline; 2) after 12-16 weeks; and 3) after another 12-16 weeks. According to Akakura et al. (*Cancer*, 1993; 71:2782-2790), serum T returns to the normal range within a median of about eight weeks (range 1-26 weeks) of stopping suppression, so that by waiting for three to four months after cessation of CAD, we can be fairly certain that serum T levels will be within normal limits for most participants even without assays. Nevertheless, we will obtain T and estradiol assays at each time point. The timing of data collection was planned, based on data on the pharmacokinetics of these interventions, in order to address our own concerns regarding this point. We will monitor subjects closely and ensure that blood is drawn and examinations are conducted at the appropriate intervals.

I am confident that this letter adequately responds to the Committee’s comments, and hope that you concur. Please contact me if you have any questions regarding our response. I look forward to hearing from you regarding the protocol.

Sincerely,

Jim Grigsby, PhD
Associate Professor, Department of Medicine (Geriatrics)
Principal Investigator

Selected Peer-Reviewed Research on Cognition

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APPENDIX H

COMMENTS FROM THE SCIENTIFIC ADVISORY COMMITTEE (SAC) OF THE UNIVERSITY'S GENERAL CLINICAL RESEARCH CENTER (GCRC)

This appendix contains the October 9, 2002 response by the Scientific Advisory Committee (SAC) of the University's General Clinical Research Center (GCRC) to the August 30, 2002 letter by Jim Grigsby, PhD (contained in Appendix G) addressing critique about the project.



General Clinical Research Center - Adult

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memo

TO: James Grigsby, Ph.D.

FROM: Tammy Manyik, GCRC Administrator 

DATE: October 9, 2002

RE: Protocol 1308 - Effects of Androgen Blockade on Cognitive Function and Quality of Life in Men with Prostate Cancer

The SAC chairman has reviewed your most recent submission of this protocol. The following issues need to be addressed before final approval can be granted.

1. The salivary cortisol levels need further justification.
2. The timing of the cognitive testing in relation to hormonal levels needs to be addressed. Broad ranges of testing intervals in many weeks does not take into consideration the bounce in hormone levels that can be seen in the last few days before the next injections. This could confound the data and could be easily controlled for by timing away from the last few days before the next injection. We, therefore, suggest that you review with Dr. Glode the pharmacology of the GnRH agonists.
3. The GCRC cannot pay for samples collected at other sites.

Please resubmit your revised protocol to Karen.esau@uchsc.edu . After the SAC chairman reviews your resubmission he will make the final determination on approval.

Thank you.

APPENDIX I

RESPONSE TO THE SCIENTIFIC ADVISORY COMMITTEE (SAC) OF THE UNIVERSITY'S GENERAL CLINICAL RESEARCH CENTER (GCRC)

This appendix contains an October 14, 2002 letter documenting Dr. Grigsby's response to continued reservations about the protocol and the assays we were requesting expressed by the Scientific Advisory Committee (SAC) of the University's General Clinical Research Center (GCRC) (see 10/09/02 memorandum contained in Appendix H).



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14 October 2002

William R. Hiatt, MD
Chairman, Scientific Advisory Committee
General Clinical Research Center

Re: Protocol 1308, *Effects of androgen blockade on cognitive function and quality of life in men with prostate cancer*

Dear Dr. Hiatt:

This is in response to the memo from Tammy Manyik, GCRC Administrator, dated 9 October 2002 and concerning the above protocol. My comments as numbered below correspond to the points in that memo.

1. *The salivary cortisol levels need further justification.* It is unclear whether the Committee desires more information on the value of cortisol levels in relation to cognition or more evidence of the appropriateness of saliva as a source of cortisol for assays. I will address both issues.

In my response to the original review, I noted that "salivary cortisol is widely used, and assays using saliva samples have been used to study a wide range of cognitive and psychological/psychiatric outcomes (e.g., Bohnen et al., 1992; Cho et al., 2001; Kozora et al., 2001; Lupien et al., 2001; Monk & Nelson, 2002; Neyla et al., 2001; Scarpa & Luscher, 2002; van Niekerk et al., 2001; Vedhara et al., 2000; Young et al., 2002). Both level of cortisol and diurnal variability have been associated with various aspects of cognition, and may be important as covariates in this study of steroids and cognition, in which the normal hormonal milieu is altered markedly by androgen suppression."

For example, Lupien et al. (2002) recently reported that glucocorticoids have a modulatory effect on memory functioning. In a repeated measures design study, the authors found that administration of metyrapone, an inhibitor of cortisol synthesis, impaired delayed recall on a word-learning test by 8% relative to a placebo. Restoration of cortisol to baseline levels by means of hydrocortisone replacement returned delayed recall performance to baseline levels. In a second experiment reported in the same paper, the authors gave subjects an injection of 35 mg hydrocortisone in the late afternoon, when endogenous cortisol concentrations tend to be at their nadir. Compared with a placebo-injection group, experimental subjects showed both faster reaction times and improved processing of stimuli on an incidental memory test. Cortisol level may adversely affect recall under some circumstances, depending on timing and absolute level (e.g., De Quervain et al., 2000; Lupien & McEwen, 1997).

The effects of cortisol on memory may reflect the distribution of glucocorticoid (type II) receptors throughout the central nervous system; in human and nonhuman primates, these are found in the neocortex, hypothalamus, entorhinal cortex, cerebellum, and hippocampus (e.g., Johnson et al., 1996; Lopez et al., 1998; Sanchez et al., 2000), all structures identified as playing important roles in different aspects of memory functioning. Glucocorticoids have been shown to affect such neural processes as involution of dendrites in the hippocampus (Woolley et al., 1990), neurotrophin expression (McLay et al., 1997), and experience-dependent synaptic plasticity (Diamond et al., 1992). The fact that these effects on cognition may be rather specific to cortisol is reflected in the finding of

Newcomer et al. (1999) that four days of cortisol administered to healthy adults caused reversible decrements in explicit verbal memory when compared with a placebo control group, while other cognitive functions were unaffected.

Heffelfinger and Newcomer (2001) recently reviewed the literature on the effects of glucocorticoids on memory functioning in different age groups. This research is important in the context of the proposed study insofar as the participants will be primarily older men. Some findings suggest that aging-related decreases in type II glucocorticoid receptor density in the brain (Bhatnagar et al., 1997), with subsequent effects on cognition. In addition, Carlson and Sherwin (1999) found that among older men and women, higher cortisol levels were related to worse performance on a measure of explicit memory, and the overall findings were noteworthy for interactions among estrogen and DHEAS levels. Given these results, in conjunction with age-related change in the hypothalamic-pituitary-adrenal axis, it appears likely that neuroendocrine feedback among older adults may be less efficient than is the case for younger adults (e.g., Raskind et al., 1994; Wilkinson et al., 1997), and hence cortisol may be an important covariate in this study.

With respect to the issue of the appropriateness of saliva as a source of cortisol, as in our previous response, salivary cortisol levels have been found to be highly correlated with serum cortisol (e.g., Cook, 2002; Gallagher et al., 2002; Gröschl et al., 2001, 2002; Kahn et al., 1988; Kirschbaum & Hellhammer, 1989, 1993; Kirschbaum et al., 1992), although it is clear that the correlation between salivary and urinary cortisol, for various reasons, is variable and in general weaker (Hurwitz et al., 2001). Putignano et al. (2001) reported that salivary cortisol levels at 8 AM, 5 PM, and midnight showed correlations of 0.50, 0.63, and 0.64 ($p < 0.0001$) with plasma cortisol levels at those same timepoints, respectively. Only when the concentration of plasma cortisol was > 500 nmol/liter did the correlation weaken. The authors went so far as to suggest that "measurement of salivary cortisol could largely replace plasma cortisol measurement" in certain situations (p. 170).

Other studies, using repeated saliva sampling throughout the day (e.g., Kirschbaum et al., 1999, 25 samples from 66 participants in a 24-hour period; Kirschbaum et al., 1994, 49 samples per day for 2 days from 20 participants; Smyth et al., 1997, 6 samples per day for 2 days from 109 participants) have found that salivary cortisol shows consistent diurnal variability in most individuals, while identifying a subsample of persons with a relatively flat curve of cortisol secretion throughout the day (see also Stone et al., 2001). For some purposes (e.g., low-dose dexamethasone suppression test), serum cortisol measurements may be preferable (Reynolds et al., 1998), while for others (examining cortisol concentrations related to exercise, as in Stupnicki & Obminski, 1992) the converse may be true. Nevertheless, a number of studies using both methods have reported that salivary and serum cortisol levels yield essentially similar experimental results, with acceptable correlations between serum or plasma and salivary cortisol levels (e.g., Aardal-Eriksson et al., 1998; del Corral et al., 1994; Gehris & Kathol, 1992; Obminski et al., 1997; Reid et al., 1992; Wedekind et al., 2000).

The primary advantage of using *salivary* cortisol rather than *serum* cortisol is that it is noninvasive, and can more easily be collected twice (morning and evening) than is the case for blood draws, decreasing the burden on participants. Although there may be some disagreement on the use of cortisol assays taken from blood or saliva, the methodology for salivary cortisol is well established and widely used, salivary assays yield essentially similar results when cortisol is used as an independent variable, and salivary cortisol has been recommended by a number of investigators (as above, and also see Raff et al., 1999; Samuels et al., 1997; Laudat et al., 1988).

2. *The timing of the cognitive testing in relation to hormonal levels needs to be addressed. Broad ranges of testing intervals in many weeks does not take into consideration the bounce in hormone levels that can be seen in the last few days before the next injections. This could confound the data and could be easily controlled for by timing away from the last few days before the next injection. We, therefore, suggest that you review with Dr. Glodé the pharmacology of the GnRH agonists.*

This is a point that previously had, in fact, been discussed in detail with Dr. Glodé. According to Dr. Glodé, patients who are on GnRH have been reported *in rare instances* to have some effect of “acute on chronic” surges in LH after administration of a GnRH agonist in the chronic setting. However, unpublished data from Praecis pharmaceutical company, which has been studying the antagonist aberelx (which is devoid of this effect) suggests that both the incidence and magnitude of this phenomenon is quite insignificant. Indeed, given the *very long time* (virtually always > 3 months) required for testosterone recovery after administration of as little as 6 months of Lupron or Zoladex, we are confident that timing of neurocognitive testing in the last few days before injections is not a problem. If the reviewer is implying that there is escape from GnRH depot injections in the last few days before the next injection, neither we, nor the FDA, are aware of this as a significant problem. This issue was examined quite extensively in the original hormonal profiles of men receiving the drug prior to approval by the FDA. Dr. Glodé, who will be consulted regarding the timing of all patient examinations, is willing to discuss this issue further with the SAC reviewers.

3. *The GCRC cannot pay for samples collected at other sites.* No justification was provided by the GCRC for this denial, and I would appreciate information about policies guiding GCRC coverage of research costs at other sites. Is the GCRC *not permitted* to reimburse investigators for such assays? Is this an NIH regulation or a local GCRC policy? To what source might one be directed for further information on this issue? As noted in my previous response, the project has no formal funding or administrative connection with the SWOG protocol to which it is a supplement. Although limited funding is available to reimburse some data collection at collaborating centers, no indirect costs are provided for them. Moreover, there are no collaborating GCRCs for this project. We originally requested that samples be obtained elsewhere according to GCRC standards and the assays be done at UCHSC, as otherwise it will not be possible to involve multiple data collection sites. Your comments on this matter would be helpful in allowing me to determine how to proceed with the current protocol, and for future reference.

Please contact me if you have any questions regarding my response. I look forward to hearing from you regarding the protocol.

Sincerely,

Jim Grigsby, PhD
Associate Professor, Department of Medicine (Geriatrics)
Principal Investigator

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APPENDIX J

**FINAL APPROVAL BY THE SCIENTIFIC ADVISORY COMMITTEE (SAC)
OF THE UNIVERSITY'S GENERAL CLINICAL RESEARCH CENTER (GCRC)**

This appendix contains notification of final approval by the Scientific Advisory Committee (SAC) of the University's General Clinical Research Center (GCRC) on October 31, 2002.



General Clinical Research Center - Adult

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October 31, 2002

Jim Grigsby, Ph.D
Box C241

Re: Protocol 1308 - Cognitive Functioning Among Men with Stage IV
Prostate Cancer Undergoing Combined Androgen Deprivation (CAD)
Therapy

Dear Dr. Grigsby:

Your protocol was approved October 31, 2002. However, please be aware that the GCRC will NOT pay for clinical lab tests performed at other sites because we do not receive credit for the visit.

The next step is to schedule a Principal Investigators (PI) Meeting so that you may discuss your study with the clinical staff in the General Clinical Research Center (GCRC). Please contact the administrative office at (303) 372-8799 between 8:00 a.m. and 5:00 p.m. any weekday with a choice of three (3) meeting times that will work for you. We will poll the staff and advise you of the date and time selected.

Before the meeting can take place, we require a copy of your IRB approval for the file. Please plan to fax this and a copy of the IRB signed consent form to the GCRC at (303) 372-5866.

A REMINDER:

The National Institutes of Health (NIH), National Center for Research Resources (NCR), requires that any publication resulting from studies conducted on the GCRC should cite the grant as a contributing source of support. Please list grant number **M01 RR00051** on any publications resulting from this protocol, and submit a copy to me at Box B141.

Sincerely,

Patricia Nash, M.S.
GCRC Administrator

APPENDIX K

NOTIFICATION TO HOSPITAL RESEARCH RESOURCES COMMITTEE (HRRC) OF APPROVAL BY THE UNIVERSITY'S GENERAL CLINICAL RESEARCH CENTER (GCRC)

This appendix contains the November 7, 2002 e-mail notification to the Hospital Research Resources Committee (HRRC) of approval by the University's General Clinical Research Center (GCRC).

Brega Angela

From: Brega Angela
Sent: Thursday, November 07, 2002 9:37 AM
To: Schumer Mary
Cc: Jim Grigsby; Patricia DeVore; Angela Brega
Subject: RE: 01-522, Androgen Blockade on Cognitive Function

Hi, Mary -

I wanted to get back to you with the information you need to finalize HRRC approval of protocol 01-522 (Effects of Androgen Blockade on Cognitive Function and Quality of Life in Men with Prostate Cancer). The GCRC has approved the protocol (see attached approval letter) and will cover the cost of all lab work associated with the project. Specifically, the following labs will be covered by the GCRC: Total T, estrone, estradiol, sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), albumin, and salivary cortisol. All participant visits will take place in the GCRC.

Please let Dr. Grigsby and me know if you need any additional information. Thank you for your assistance.

Angela



Approval-ltr.doc

Angela G. Brega, Ph.D.
Center for Health Services Research
University of Colorado Health Sciences Center
1355 South Colorado Boulevard, Suite 306
Denver, CO 80222
phone: (303) 756-8350 fax: (303) 759-8196
e-mail: Angela.Brega@uchsc.edu

-----Original Message-----

From: Schumer Mary
Sent: Wednesday, February 27, 2002 10:51 AM
To: Grigsby Jim; Brega Angela
Subject: 01-522, Androgen Blockade on Cognitive Function

Drs. Grigsby and Brega:

The above study will be approved by the HRRC pending the following:

1. Confirmation of GCRC approval with the services covered defined
2. Clarification of the site of study participant's visits? Will the study participants be seen in the clinic or on the GCRC?

Thanks,

Mary Schumer, MS, CPA
Research Administration
University of Colorado Hospital
Phone: 303-372-4067
FAX: 303-372-4064
e-mail: mary.schumer@uhcolorado.edu

APPENDIX L

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD (COMIRB) AMENDMENT AND ALTERATION(S) SUBMISSION

This appendix contains the January 8, 2003 Amendment and Alteration(s) Form submission to the Colorado Multiple Institutional Review Board (COMIRB) presenting newly developed recruitment materials and the addition of Western Urologic Research Center in Wheat Ridge, Colorado as a new site for patient referrals.



University of Colorado Health Sciences Center

Office of the Chancellor
Center for Health Services Research

1355 So. Colorado Blvd., Suite 306
Denver, Colorado 80222
(303) 756-8350
FAX: (303) 759-8196

January 8, 2003

Colorado Multiple Institutional Review Board
University of Colorado Health Sciences Center
Mail Stop F-490
P.O. Box 6508
Aurora, CO 80045-0508

Re: **COMIRB Protocol 01-522**, *Cognitive functioning among men with stage IV prostate cancer undergoing combined androgen deprivation (CAD) therapy*

Dear Reviewer:

Enclosed are an Alterations and Update(s) Form along with copies of subject recruiting materials that we propose to use in the above protocol. The first subject recruiting material is a newly developed letter (advertisement) to be sent to patients of Dr. Michael Glodé, Co-Investigator on the protocol, and to patients of Western Urologic Research Center, of Wheat Ridge, CO, which is interested in participating in the study. The second represents very minor modifications to an advertisement (previously approved by COMIRB) that can be given to patients when they are being seen in the clinic. The third is a form (questionnaire) that will be used not only to ensure that study eligibility criteria and protocols are followed, but also to collect patient demographic information at study admission. We are requesting review of these materials.

Also, we would like to notify COMIRB that Western Urologic Research Center intends to collaborate in this study by referring patients to the study. We have marked the box entitled "Personnel/Site Change" on the attached Alterations and Update(s) Form. The contact person at Western Urologic Research Center will be Eric Carlson, BS, CCRC, who is the Clinical Research Coordinator for the organization. His telephone number is 303 421 5783. Mr. Carlson has been informed of the requirement for human subjects education, and is arranging to complete COMIRB 101 and 201. I would appreciate knowing whether any additional steps are required to amend the protocol in order to include Western Urologic Research Center.

Thank you for your attention.

Sincerely,

Jim Grigsby, PhD
Associate Professor, Department of Medicine
Principal Investigator

Patricia A. DeVore
Study Coordinator

Section 1

COMIRB Forms

Alterations and Update(s) Form

Date: 01-06-03	COMIRB #: 01-522	Campus Box: C-241	Contact: Patricia DeVore
Title: Cognitive Functioning Among Men With Stage IV Prostate Cancer Undergoing Combined Androgen Deprivation (CAD) Therapy			
Principal Investigator Name: Jim Grigsby, PhD			

Type of Alteration or Update (Please check *all* boxes that apply):

- Consent Form Revision
- Advertisement / Advertisement Revision
- Questionnaire / Questionnaire Revision
- Personnel / Site Change
- Project Title Change
- Other

Description of Alteration or Update:

- Advertisement: Development of a Volunteer Recruitment Letter,
- Advertisement Revision: Minor modifications to a Volunteer Advertisement previously approved by COMIRB,
- Questionnaire: Development of a Subject Recruitment and Eligibility Form, and
- Site Addition: Western Urologic Research Center in Wheat Ridge, CO will be referring patients to the study.

Attachment(s) Attach all supporting documents and list attachments here:

- cover letter,
- newly developed Volunteer Recruitment Letter,
- revised advertisement entitled "Volunteers with Prostate Cancer Needed for Quality of Life Research Study," and
- newly developed Subject Recruitment and Eligibility Form.



Investigator's Signature
(All correspondence must have PI or Co-PI signature)

For COMIRB Office use only

Chair Recommendations:

Protocol Revision is a Minor Change Approved Minor Modifications Required
Deferred to Full Committee

Chairperson, COMIRB

- Steve Bartlett, R.Ph.
- Cornelis Rietmeijer, M.D.
- Adam Rosenberg, M.D.
- Norman H. Stoller, DMD
- Ken Easterday, R.Ph.

Date

- David Lawellin, Ph.D.
- Hans Neville, M.D.

Section 2

Subject Recruitment Materials

Volunteer Recruitment Letter

(newly developed)

This letter (advertisement) will be sent to patients of Dr. Michael Glode, and to patients of Western Urologic Research Center in Wheat Ridge, CO.

Dear _____,

I am writing to inquire whether you would be interested in participating in a research study of quality of life among men receiving androgen blockade treatment for prostate cancer. Androgen blockade refers to hormonal treatment of cancer, and we are especially interested in men who are on lupron, zoladex, and/or antiandrogens, either continuously, or as part of an intermittent treatment regimen. This study is being conducted at the University of Colorado Health Sciences Center.

Some men who have taken these medications for prostate cancer report that they think they might have difficulty with such abilities as attention and memory, and we would like to study this in more detail to see whether problems of this sort might be associated with androgen blockade, and how significant these problems might be. The purpose of this research therefore is to study whether memory, concentration, or other thinking abilities are affected by the treatment, and whether this might have an influence on quality of life. If the results show that some men are affected in this way by androgen blockade, it might be possible to devise treatments that would diminish the significance of this effect.

If you agree to participate, it would require between an hour and a half to two hours of your time on three different occasions. These sessions would be separated by about four to six months, and each time you are seen it would involve collecting a small amount of blood and saliva, and having you complete some tests of memory, attention, and other problem solving abilities. The testing will take place at the General Clinical Research Center at University of Colorado Hospital at 9th Avenue and Colorado Boulevard in Denver.

We are looking for men aged 50 years and older, who are on one of these treatment regimens, who have not had an orchiectomy, and who are not on any other adjuvant chemotherapy.

If you think you might be interested in participating in this research study, you can call either me, or the principal investigator of the study, Jim Grigsby, PhD. Dr. Grigsby's telephone number is (303) 756-8350. One of us can provide you with more information and, if you are interested, an informed consent form that provides details about what participation would involve. If you have any questions about the research, what it would mean if you were involved, or your rights as a participant, please call one of us.

Thank you very much for considering this request.

Sincerely,

Clean Copy of Revised Volunteer Advertisement

**This advertisement will be given to patients seen in either
Dr. Michael Glode's clinic or at the Western Urologic
Research Center in Wheat Ridge, CO.**

Volunteers with Prostate Cancer Needed for Quality of Life Research Study

Protocol # 01-522 Cognitive functioning among men on hormone therapy for prostate cancer

We are looking for volunteers who are willing to donate about 90 to 120 minutes on each of 3 occasions, approximately four to six months apart, to take some tests of memory, concentration, and thinking, and to give a small sample of blood and saliva. The purpose of this research is to determine the effects of androgen (testosterone) on mental abilities and on quality of life. We are interested in studying this issue because many men report difficulties with thinking or memory after they start hormone blockade therapy.

We need men who are on intermittent or continuous androgen blockade therapy, and volunteers who may not have prostate cancer but who could act as age-matched control subjects (not taking hormone treatments).

We are not able to use men who have had orchiectomy or are on current other adjuvant treatments such as chemotherapy. In other words, we are looking primarily for patients who are on lupron, zoladex, and/or antiandrogens.

To obtain further information, determine whether you might wish to participate, or request a consent form with more details, please call:

**Jim Grigsby, PhD
(303) 756-8350**

Subject Recruitment and Eligibility Form

This form (questionnaire) will be used at study admission to ensure that study eligibility criteria and protocols are met. In addition, this form will be used to collect patient demographic information.

Fax to: Patricia DeVore
Fax: (303) 756 4255
Phone: (303) 756 8350

The information contained in this FAX message is intended only for the personal and confidential use of the designated recipient. This message is restricted in use to a legitimate business purpose and as such is privileged and confidential. If the reader of this message is not the intended recipient or an agent responsible for delivering it to the intended recipient, you are hereby notified that you have received this documentation in error, and that any review, dissemination, distribution or copying of this message is strictly prohibited. If you have received this communication in error, please notify us immediately by telephone and return the original message to us by return mail. Thank you.

Cognitive Functioning Among Men with Stage IV Prostate Cancer Undergoing Combined Androgen Deprivation (CAD) Therapy

Subject Recruitment and Eligibility Form

All Study Patients (both subjects and controls):

- Age 50 or older
- Fluent English speakers

Inclusion Criteria (please check all that apply):

- Adenocarcinoma of the prostate, with or without metastases to bone, brain, liver, or lung
- Elevated PSA (5 ng/mL or greater)
- Continuous or intermittent androgen deprivation therapy (e.g., lupron, zoladex, antiandrogens)
- At least one year since any prior neoadjuvant or adjuvant hormonal therapy or prior finasteride

Exclusion Criteria (please check all that apply):

- Concurrent biological response modifier therapy or chemotherapy; concurrent hormonal therapy
- Concurrent radiotherapy other than palliation of painful bone metastases
- Bilateral orchiectomy
- Active medical illness precluding treatment or limiting survival
- Second malignancy within five years *except* adequately treated nonmelanomatous skin cancer, in situ bladder cancer or other superficial cancer
- History of neurologic disorder, head trauma with loss of consciousness, learning disability, mental retardation, alcoholism, or psychosis

Recruitment Checklist (please check all that apply):

- Explained study to patient
- Obtained informed consent from patient
- Copy of informed consent given to patient
- Explained to patient that Research Center will coordinate scheduling
- Flyer given to patient
- Faxed informed consent to Research Center (303 756 4255)
- Original informed consent mailed to Research Center (Campus box C-241)
- Copy of informed consent placed in patient clinic chart

Patient Information (please print):

Patient Name: _____

Patient ID Number: _____

Date of Birth: ____ / ____ / ____

Date Consent Signed: ____ / ____ / ____

Home Phone Number: (____) _____

Alternate Phone Number: (____) _____

Street Address: _____

City: _____ State: _____ ZIP: _____

APPENDIX M

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD (COMIRB) REQUEST FOR PROTOCOL CHANGES

This appendix contains a copy of the January 16, 2002 request for changes by the Colorado Institutional Review Board (COMIRB) to the study protocol to incorporate explanation of the newly developed recruitment materials and the addition of Western Urologic Research Center as a site for patient referrals.



Colorado Multiple Institutional Review Board
13001 E. 17th Place
Building 500, Room N3214
Aurora, Colorado 80010-7238

Mailing Address:
Mail Stop F-490
P O Box 6508
Aurora, Colorado 80045-6508

(303) 724-1055 [Phone]
(303) 724-0990 [Fax]
comirbweb.uchsc.edu [Web]
comirb@uchsc.edu [E-Mail]
Assurance # M-1494-01

University of Colorado Hospital
Denver Health Medical Center
Veteran's Administration Medical Center
The Children's Hospital
University of Colorado Health Sciences Center
Colorado Prevention Center

DEVORE PATRICIA

January 20, 2003

01/21/2003

To: JIM GRIGSBY

From: Colorado Multiple Institutional Review Board

Subject: **COMIRB Protocol 01-522
Update Review (UPD003)
1st Review**

Title:

EFFECTS OF ANDROGEN BLOCKADE ON COGNITIVE FUNCTION AND QUALITY OF
LIFE IN MEN WITH PROSTATE CANCER

Review/Panel: **Chair Review / Panel A**

Review Date: 16 January 2003

Protocol Update Requires Minor Modifications

Stipulated changes in the Protocol Update are needed. These are described in the comments below. To facilitate a timely review, please provide a **cover letter** itemizing your response to each issue the reviewer has asked you to address. Please provide an edited copy of the Protocol/Protocol summary (if applicable), and/or Consent Form (if applicable), with highlighted changes and a clean copy of the Consent Form for the Co-Chair signature.

If the modifications are not received in COMIRB by the protocol's expiration date (**06/26/2003**), your Protocol Update will be **WITHDRAWN**. Implementation of this change may not begin until final approval is received.

Comments:

Added site to the description of recruitment methods.

How will Western Urologic Research Center be referring subjects: Two appropriate methods would be:-

1. Patients can be informed of study and if interested can contact study personnel or,
2. If patient authorizes a staff member providing care to call study personnel.

It would be inappropriate to get a list of all qualifying patients @ WURC and for you to contact them.

Subject Recruitment and Eligibility Form - Form OK - subject has consented to participate in study so OK to send patient's info to coordinator.

Volunteers with Prostate Cancer - Advertisement - OK no changes required.

Letter - On 3rd paragraph Instead of "hour and a half to two hours" Please put - 90-120 minutes (to be consistent with advertisement).

Ken Easterday, RPh, Co-Chair
Cornelis Rietmoller, MD, Co-Chair

Norman Stoller, DMD, Co-Chair
Hans Neville, MD, Co-Chair

Adam Rosenberg, MD, Co-Chair
Dave Lawellin, PhD, Co-Chair

Steve Bartlett, RPh, Co-Chair

Revised 09/02

01-522 Panel: A Expedited



Colorado Multiple Institutional Review Board
13001 E. 17th Place
Building 500, Room N3214
Aurora, Colorado 80010-7256

Mailing Address
Mail Stop F-490
P O. Box 6508
Aurora, Colorado 80045-6508

(303) 724-1055 [Phone]
(303) 724-0990 [Fax]
comirbweb.uchsc.edu [Web]
comirb@uchsc.edu [E-Mail]
Assurance # M-1494-01

University of Colorado Hospital
Denver Health Medical Center
Veteran's Administration Medical Center
The Children's Hospital
University of Colorado Health Sciences Center
Colorado Prevention Center

DR. VORE, PATRICIA
Campus Box 0241

01/21/2003

Please clarify the use of this recruitment letter:-

1. Are these patients of one of the investigator's?
2. Update the Protocol Summary to describe the use of a recruitment letter.
3. Who is the letter from?

Any questions about the COMIRB's action on this study should be referred to COMIRB at 303-724-1055 or UCHSC Box F-490.

Ken Easterday, RPh, Co-Chair
Cornells Rietmeijer, MD, Co-Chair

Norman Stoller, DMD, Co-Chair
Hans Naville, MD, Co-Chair

Adam Rosenberg, MD, Co-Chair
Dave Lawellin, PhD, Co-Chair

Steve Bartlett, RPh, Co-Chair

Revised 09/02

01-522 Panel: A Expedited

APPENDIX N

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD (COMIRB) PROTOCOL AMENDMENT AND PROTOCOL UPDATE SUBMISSION

This appendix contains a copy of the January 28, 2002 protocol revisions submitted to the Colorado Multiple Institutional Review Board (COMIRB) in response to the January 14, 2002 request for changes to the study protocol (see Appendix M).

Center for Health Services Research

1355 So. Colorado Blvd., Suite 306
Denver, Colorado 80222
303-756-8350
FAX 303-759-8196

January 29, 2003

COMIRB Coordinator
Colorado Multiple Institutional Review Board
13001 East 17th Place
Building 500, Room N3214
Aurora, Colorado 80010-7238

Dear COMIRB Coordinator:

RE: Resubmission of Alterations and Updates for COMIRB Protocol 01-522

The 01/16/03 comments by Ken Easterday, RPh, on our Alterations and Updates submission for COMIRB Protocol 01-522 indicate that "to facilitate a timely review, please provide a cover letter itemizing your response to each issue the reviewer has asked you to address." In addition, an edited copy of the Protocol/Protocol Summary with highlighted changes and a clean copy for the Co-Chair signature should be included. The attached package is intended to satisfy the requirements for revisions to COMIRB Protocol 01-522.

Each comment by Ken Easterday, RPh, is addressed point by point in the following list.

- a. **Add site to the description of the recruitment methods.** We added a brief description of Western Urologic Research Center to the second paragraph of the "Recruiting Methods" subsection on page 4 of the Protocol Summary.
- b. ***How will Western Urologic Research Center be referring subjects? Two appropriate methods would be: 1) Patients can be informed of study and if interested can contact study personnel, or, 2) If patient authorizes a staff member providing care to call study personnel. It would be inappropriate to get a list of all qualifying patients at WURC and for you to contact them.*** To address this point, we added several sentences about the method for referring subjects from Western Urologic Research Center to the "Recruiting Methods" subsection on page 4 of the Protocol Summary. In addition, we added a sentence to the "Consent Procedures" subsection on page 5 of the Protocol Summary. Patients from Western Urologic Research Center will be informed of the study and if interested can contact study personnel. See highlighted section on the Protocol Summary. A clean copy of the Protocol Summary has been provided for the Co-Chair to sign and stamp with the approval date.
- c. ***Subject Recruitment and Eligibility Form -- Form OK -- subject has consented to participate in study so OK to send patient's info to coordinator.*** COMIRB please have Co-Chair sign and stamp the Subject Recruitment and Eligibility Form with approval date.
- d. ***Volunteers with Prostate Cancer -- Advertisement -- OK no changes required.*** COMIRB please have Co-Chair sign and stamp the Volunteers with Prostate Cancer advertisement with approval date.
- e. ***Letter -- On 3rd paragraph instead of "hour and a half to two hours," please put "90-120 minutes" to be consistent with advertisement.*** We changed the Letter to address this concern. See clean copy for the Co-Chair to sign and date.

January 29, 2003

Page 2

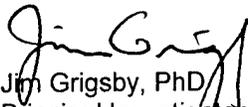
f. **Please clarify the use of this recruitment letter:**

1) Are these patients of one of the investigator's? Many of the patients will be Dr. Glodé's, one of the principal investigators, from the University of Colorado Cancer Center. Other patients will be from one of the six physicians affiliated with Western Urologic Research Center. This point is addressed in the cover page entitled "Volunteer Recruitment Letter (newly developed)" in Section 2, "Subject Recruitment Materials." *"This letter (advertisement) will be sent to inform eligible patients already on androgen blockade about the study. This letter will be sent by either Michael Glodé, MD of the University of Colorado Cancer Center or by Eric Carlson of Western Urologic Research Center (WURC) in Wheat Ridge, CO. ..."*

2) Update the Protocol Summary to describe the use of a recruitment letter? A new paragraph was added to the "Recruiting Methods" subsection on page 4 of the Protocol Summary. See highlighted section on the Protocol Summary. A clean copy of the Protocol Summary has been provided for the Co-Chair to sign and stamp with the approval date.

3) who is the letter from? The Recruitment Letter will be from Michael Glodé, MD at the University of Colorado Cancer Center or from Eric Carlson, Director of Operations at Western Urologic Research Center in Wheat Ridge. See sample letters in the "Volunteer Recruitment Letter (newly developed)" subsection of the section entitled "Subject Recruitment Materials."

Sincerely,



Jim Grigsby, PhD
Principal Investigator

Associate Professor, Department of Medicine (Geriatrics), University of Colorado Health Sciences Center

Protocol Amendment(s) Form

The Protocol Amendment Form in this section includes minor changes requested by COMIRB on 01/16/03. These minor changes include a discussion of how Western Urologic Research Center will refer patients to the study and how the recruitment materials will be used.

Protocol Amendment(s) Form (Includes: Amendments, Protocol Revisions and/or Addendums)

Date: 01-27-03	COMIRB #: 01-522	Campus Box: C-241	Contact: Patricia DeVore
Title: Cognitive Functioning Among Men With Stage IV Prostate Cancer Undergoing Combined Androgen Deprivation (CAD) Therapy			
Principal Investigator Name: Jim Grigsby, PhD			

Amendment Description Please describe the amendment(s) to the protocol and attach a copy of the amendment(s) to this form.

- This amendment includes a change in enrollment number.
 The current number of approved local subjects is _____.
 The requested change is _____. The new requested total is _____.
 (Please include justification for change in enrollment number.)

The Co-Chair that reviewed an Alterations and Update(s) submission for COMIRB Protocol 01-522 requested that we update the Protocol Summary to describe both the addition of a new site and the use of a recruitment letter. A new paragraph was added to the "Recruiting Methods" subsection on page 4 of the Protocol Summary and a new sentence was added to the "Consent Procedures" subsection on page 5 of the Protocol Summary to address this request. See highlighted version of the Protocol Summary attached. A clean copy of the revised Protocol Summary is also attached for the Co-Chair to sign and date.

Please check the appropriate boxes below:

- Revised highlighted protocol summary is attached. **OR**
 Amendment does not affect protocol summary.
 New consent form and alteration/update form are submitted. **OR**
 Amendment does not affect consent form.



Investigator's Signature
 (All correspondence must have PI or CO-PI signature)

For COMIRB Office use only

Chair Recommendations:

Protocol Amendment is a Minor Change **Approved** **Minor Modifications Required** **Deferred to Full Committee**

Protocol Amendment requires Consent Form Change(s) **Yes** **No**

Chairperson, COMIRB

- Steve Bartlett, R.Ph.
 Cornelis Rietmeijer, M.D.
 Adam Rosenberg, M.D.

Date

- Norman H. Stoller, DMD
 Ken Easterday, R.Ph.
 David Lawellin, Ph.D.
 Hans Neville, M.D.

Revised Highlighted Protocol Summary

(revised 01/27/03)

COMIRB requested minor changes to the Protocol Summary on 01/16/03. These changes include a discussion of how Western Urologic Research Center will refer patients to the study and how the recruitment materials will be used.

**Cognitive Functioning Among Men with Stage IV Prostate Cancer Undergoing
Combined Androgen Deprivation (CAD) Therapy**

COMIRB Protocol 01-522

Jim Grigsby, PhD, Principal Investigator

Co-Investigators:

Angela Brega, PhD

Mike Glodé, MD

Wendee Gozansky, MD

Peter Shaughnessy, PhD

Protocol Revised 27 January 2003

BACKGROUND

The proposed pilot study is a supplement to the NCI-funded study, *Phase III randomized study of intermittent versus constant combined androgen deprivation (Bicalutamide and Goserelin) in patients with Stage IV prostate cancer responsive to such therapy*. That study, previously approved by COMIRB (COMIRB Protocol Number 95-279), also carries the following protocol ID numbers: SWOG-9346, CAN-NCIC-JPR8, CLB-9594, INT-0162. This proposed study has been assigned COMIRB protocol number 01-522.

In that study, following an initial induction phase involving 8 courses (7 months) of combined androgen deprivation (CAD) therapy, patients are randomized to one of two arms. Patients assigned to the first arm receive continuous CAD, even in the absence of disease progression (as determined by level of prostate specific antigen, or PSA). Those individuals assigned to the second arm, following the induction phase, discontinue CAD therapy and are observed until either their PSA rises to approximately 20 ng/mL or they show clinical signs of progressive disease. At that time, patients resume CAD for a second round of 8 courses (7 months), after which time, if PSA is within normal limits, CAD is again discontinued.

This proposed study involves no intervention. It is a study of certain aspects of the quality of life of men on an androgen deprivation protocol for treatment of Stage IV prostate cancer. The subjects will be either prostate cancer patients or healthy controls. The prostate cancer patients will be recruited from among men who are either enrolled in one of the above experimental protocols, or who are not enrolled in an experimental protocol but are receiving treatment essentially similar to that used in the protocols. The only requirements of participants in this study are: 1) cognitive assessment, 2) blood samples, and 3) completion of mood and quality of life instruments. Each of these will be conducted at three timepoints. Our proposed protocol is described in detail below.

Intermittent vs. Continuous Combined Androgen Deprivation Therapy

Prostate cancer has been found to grow rapidly in the presence of androgens, but conditions of androgen suppression induce apoptosis and lead to regression in tumor size. This therapy, which is used primarily with men with advanced disease, appears to result in reasonably good short-term management, but long-term outcome is essentially unchanged. Over time, the tumors tend to become androgen-independent, so that medical castration eventually has little beneficial effect. While continuous CAD is considered a viable approach to the treatment of Stage IV prostate cancer, there are two major drawbacks. First, there are data suggesting that continuous therapy may lead to relatively rapid development of androgen independence. Second, an androgen deprivation syndrome develops concomitant with the suppression of serum androgens, and this is associated with deleterious effects on quality of life. Herr and O'Sullivan (2000) reported that men on androgen suppression, compared with those not on CAD, reported greater fatigue, less energy, greater emotional distress, and a lower quality of life overall. Patients treated by the co-PI at University of Colorado Hospital also report problems with cognitive functioning, but the nature of any such difficulties is not understood.

The use of intermittent CAD as an alternative to continuous androgen suppression has been shown to improve quality of life, reduce toxicity, facilitate recovery of libido and erectile functioning, and slow tumor

progression to an androgen-independent state by allowing some apoptotic recovery (Crook et al., 1999; Goldenberg et al., 1995, 1999; Higano et al., 1996; Wolff & Tunn, 2000). The NCI-funded Phase III trial for which the proposed study is a supplement was designed to provide data regarding the effectiveness of the continuous and intermittent approaches to treatment, with survival, PSA levels and changes, and several indices of quality of life as endpoints. In this supplement, we expand the scope of quality of life outcomes to include several specific aspects of cognitive functioning.

Sex Steroids and Cognition

In addition to findings of adverse effects reported in the literature, anecdotal reports by patients treated with continuous CAD at University of Colorado Hospital suggest that there may be a relatively high prevalence of cognitive impairment among this population. This has not previously been reported in the literature and is the focus of this proposed investigation. Our goal is to study whether cognitive impairment occurs, to determine the nature of such dysfunction, and to evaluate its relationship to hormonal status.

The mechanism(s) by which CAD may interfere with cognitive functioning, as well as the nature of such impairment, are suggested by the scientific literature. Such effects could possibly be a result of the fatigue and dysphoric mood that often accompany CAD, as either of these could disrupt the speed and capacity of information processing with consequent deleterious effects on sustained attention, learning, memory, and complex problem solving. It has been demonstrated, however, that certain sex steroids appear to have relatively direct effects on circumscribed aspects of cognition (for recent reviews see Erlanger et al., 1999; Henderson, 1997; Kimura, 1999; Sherwin, 1994a, b). Although the molecular means by which this is accomplished are not well understood, it appears that there are two primary mechanisms: 1) steroids influence the function of neurons by binding to intracellular receptors regulating gene expression; and 2) they function as neuromodulators, affecting the activity of ligand-gated channels and of specific classes of receptors coupled to G-proteins (Kelly & Wagner, 1999; Levin, 1999; Rupprecht & Holsboer, 1999; Wagner et al., 2001). Estrogen in particular appears to have neuromodulatory effects at cholinergic, noradrenergic, serotonergic, and GABAergic synapses.

Much of the research to date has focused on estrogen, on its general effects on cognition (e.g., Steffens et al., 1999, used the Mini Mental State Exam), and possible role as a neuroprotectant in Alzheimer's disease (Henderson, 1997; Honjo et al., 1989; Ohkura et al., 1994). A number of studies, however, have focused on specific aspects of cognition, with a particular emphasis on verbal fluency, fine motor tasks, and learning and memory. For example, it has been found that pre-menopausal women, acting as their own controls, show superior verbal fluency and fine motor functioning when estrogen levels are higher (as in the midluteal phase of the menstrual cycle) than when estrogen levels are lower. Post-menopausal women taking estrogen and women who are hypoestrogenic from taking GnRH agonists but taking "add-back" estrogen (Sherwin & Tulandi, 1996), compared with those not on estrogen, show similar results and experience beneficial effects on memory functioning (Baker et al., 2000; Hampson, 1990a, 1990b; Hampson & Kimura, 1988; Phillips & Sherwin, 1992; Sherwin, 1988, 1999). Even among healthy young men, higher levels of estradiol were associated with superior performance on measures of visual memory (Kampen & Sherwin, 1996). Such results have been obtained even among women with Alzheimer's disease (Asthana et al., 1999a, 1999b, 1999c). Not all findings have been positive, however. For example, Barrett-Connor and Goodman-Gruen (1999) reported no relation between endogenous estrogen level and any measure of cognition among a sample of older women not on hormone replacement therapy (although they also reported a relation between higher levels of testosterone (T) and two cognitive measures); however, in that study the assays were conducted on blood drawn several years prior to the cognitive assessment. Overall, the findings of improved cognitive function with increased estrogen levels have generally been consistent.

The effects of androgens on cognition have been less well characterized, although there is evidence that T is important for certain aspects of cognition. The strongest support comes for the role of T on tasks involving a strong spatial component, such as judging line orientation or mentally rotating visual images (Janowsky et al., 1994; Kimura, 1999; Van Goozen et al., 1995). Testosterone levels vary during the course of the day and across seasons, and moderate, but not low or high levels of T, are associated with better performance on tests of spatial ability (Kimura & Hampson, 1994; Moffat & Hampson, 1996). A recent report (Janowsky et al., 2000) suggested

that working memory for visual material was improved by T supplementation among healthy older men, although working memory was unaffected among older women given estrogen supplements. An earlier study of 33 young men (with T levels in the normal range), however, found T levels unrelated to memory performance (Janowsky et al., 1998). There have been no studies reported in the literature examining changes in cognitive function in men undergoing CAD therapy such as the one we propose here.

Given that: 1) sex steroids influence the performance of a number of different kinds of cognitive tasks; 2) these effects appear to be mediated by neuromodulation and gene expression in the brain; and 3) androgen blockade must necessarily disrupt the influence of both androgens and estrogens at the neuronal level, there is a compelling need to investigate the relations among CAD, sex steroid levels, and performance on tasks that have been shown to be influenced by the plasma level of either estrogens or androgens. Importantly, cognitive impairment has frequently been shown to be associated with poorer quality of life (e.g., Lloyd et al., 2000; Moore et al., 2000; Schrag et al., 2000). This may be the case especially among older adults, for whom cognitive impairment may be associated with impaired performance of activities of daily living (ADL), instrumental ADLs, and reduced independence (Grigsby et al., 1998; Kaye et al., 1990). The proposed research thus is poised to contribute significantly to an understanding of an important factor affecting quality of life (QOL) among men with prostate cancer and to better illuminate the influence of androgens on specific aspects of cognition.

STUDY OBJECTIVES

This protocol is for a proposed study submitted to the Department of Defense as a New Investigator Award Proposal, under the Department of Defense Congressionally Directed Medical Research Program (CDMRP) for prostate cancer. That proposed study is relevant to the *Prostate Cancer Research Program Fiscal Year 2001 Program Announcement* insofar as the results would contribute to improvement in “the quality of life for individuals and their families living with prostate cancer” by addressing a previously neglected issue: the effects on cognition and quality of life of hormone therapy for prostate cancer. We have requested funding for a period of 36 months.

The major purpose of this study is to add significant new knowledge to the field of prostate cancer research and improve the QOL for men with this illness. We will examine cognitive functioning to elucidate the presence, nature, and severity of cognitive deficits among men undergoing CAD therapy and to assess and quantify the relationship of any such deficits to plasma levels of sex steroids. Our hypotheses and specific aims are based on the premise that androgen blockade interferes with neuromodulatory processes and gene regulation that influence performance on specific cognitive tasks. The proposed project has the following specific aims. We intend to:

- assess whether there is evidence of cognitive impairment among patients on CAD therapy;
- assess the nature and severity of that impairment, evaluating different aspects of cognition;
- use cognitive tests sensitive to fluctuations in levels of T or estrogen, and others that are unaffected by plasma sex steroid level, to evaluate whether the deficits observed are related directly to changes in the level of T, the level of estradiol, or of both;
- obtain plasma levels of T and estradiol at each data collection time point in order to evaluate the relationships between performance on specific cognitive tests and levels of these sex steroids; and
- examine the relationship between performance on cognitive measures and QOL.

The hypotheses associated with our major purpose and specific aims are as follows:

- a. Androgen deprivation therapy has a negative effect on cognitive functioning in men with prostate cancer. More specifically, this will be examined by testing the following two subhypotheses:
 - 1) Performance on selected measures of cognition will be worse for prostate cancer patients on CAD than for subjects not on CAD who have normal levels of T (this includes controls and off-treatment intermittent CAD patients), after controlling for fatigue and depression.
 - 2) Patients on both continuous and intermittent, on-treatment, CAD protocols will perform worse on cognitive measures than will age-matched healthy controls, after controlling for fatigue and depression.
- b. Performance on working memory and visual-spatial tests will be associated with plasma T level.

- c. Performance on verbal fluency and verbal learning and memory tests will be associated with plasma estradiol level.
- d. Performance on tests previously not shown to be affected by sex steroid levels (e.g., verbal reasoning) will remain unaffected by CAD.
- e. Poor performance on measures of cognitive functioning will be correlated with poor QOL as measured by the SF-36.

Hypothesis *a* is the primary study hypothesis. To the extent that it is validated through empirical testing, the results of testing the remaining four hypotheses (*b* through *e*) will reveal further how and why the relation in hypothesis *a* is effectuated.

METHODS

Overview

The research we propose will involve a prospective cohort study of prostate cancer patients receiving either continuous or intermittent CAD therapy. They will be compared with each other, and with a matched group of healthy control subjects, at each of three time points. In addition, within-subject performance of intermittent CAD patients will be analyzed, using patients as their own controls, to determine whether CAD is responsible for observed cognitive deficits. Each subject will be examined using a battery of cognitive tests and will be asked to give a blood sample on each occasion for measurement of T and estradiol levels.

This study will be conducted as a supplement to SWOG protocol 9346, which was discussed in the introduction. In that study, following an initial induction phase involving eight courses (seven months) of CAD therapy, Stage IV prostate cancer patients are randomized to one of two arms. Patients assigned to the first arm receive continuous CAD, even in the absence of disease progression (as determined by level of PSA). Individuals assigned to the second arm, following the induction phase, discontinue CAD therapy and are observed until either their PSA rises to approximately 20 ng/mL or they show clinical signs of disease activity. At that time, patients resume CAD for a second round of eight courses (seven months), after which time, if PSA is within normal limits, CAD is again discontinued. We propose to use patients already participating in both the intermittent and continuous arms of this SWOG protocol. The present study involves no additional treatment of patients on these protocols, and will not affect their treatment in any way. It is intended only to evaluate possible effects of that treatment on cognition.

Recruiting Methods

Subjects will be males aged 50 and older who meet the inclusion and exclusion criteria for the clinical trial. CAD subjects will be recruited from centers participating in SWOG protocol 9346. We will recruit as many as possible from the University of Colorado Hospital, but will have access to patients being treated in other centers as well. Second, some participants will be enrolled who are being treated with one of the two regimens off-protocol by Dr. Glodé. These subjects will meet the inclusion and exclusion criteria of the SWOG protocol.

During a routine office visit, eligible patients at the University of Colorado Hospital and at other participating centers will be provided with an advertisement soliciting volunteers. Eligible patients from Western Urologic Associates, a freestanding, autonomous private practice in Wheat Ridge, Colorado, will be recruited by physician and nurse directed referrals to the research staff at Western Urologic Research Center (WURC), a research center within Western Urologic Associates. Additional patients from WURC may be identified by database searches, and chart reviews. Patients at University of Colorado Hospital, other participating centers, and WURC who are already on androgen blockade will be sent a recruitment letter by their physician informing them about the study. Patients who are interested in participating can contact either their physician or study personnel.

Healthy controls, matched on age (within five years) and education (within two years), will be recruited from the community. To minimize genetic and socioeconomic variance, we will first attempt to recruit brothers of patients who participate in the study. Control subjects also may be recruited from among the brothers of prostate cancer patients who participate in local support groups but who do not participate in the study. We have close contacts with several such groups. On the basis of power calculations (discussed below), we have

determined that we will need approximately 22 subjects per group for mean comparisons with $\alpha = 0.05$, and 31 subjects per group if $\alpha = 0.01$. To deal with the likelihood of attrition due to mortality, exacerbation of prostate cancer, exacerbation of other chronic illnesses, development of new acute illnesses, and other factors that might affect this predominantly older sample, we plan to recruit 35 subjects per group.

Consent Procedures

Consent will be obtained by Dr. Glodé, or by a clinical research associate at UCHSC who is thoroughly familiar with the clinical trial protocol. At other sites, consent will be obtained by that site's principal investigator under the SWOG/NCI/ECOG protocol. The exception to this will be Western Urologic Research Center in the Denver area at which patients will be informed of the study by the Director of Operations or one of six physicians at the time of a routine office visit and, if interested, the patient can contact study personnel. Consent will be sought in the clinic during a routine clinic appointment and the patient (or control) will be given time to consider the research and whether he wishes to participate. After receiving information on the study (verbally conveyed or by either the recruitment letter or the advertisement), he will be given an opportunity to ask questions and inquiries will be made to determine whether he fully understands the requirements of participation and his rights as a subject. After signing an informed consent form, the subject will be given a copy of the consent and his original consent will be documented in his clinic chart.

Inclusion and Exclusion Criteria

All participants will be men aged 50 and older, fluent English speakers, and willing to provide informed consent for participation. Subjects with prostate cancer will conform to the inclusion and exclusion criteria for the CAD clinical trial. As these are quite detailed, they will only be summarized here.

- Adenocarcinoma of the prostate, with or without metastases to bone, brain, liver, or lung;
- Elevated PSA (5 ng/mL or greater);
- No concurrent biological response modifier therapy or chemotherapy; no concurrent hormonal therapy; and at least one year since any prior neoadjuvant or adjuvant hormonal therapy, or any prior finasteride;
- No concurrent radiotherapy other than palliation of painful bone metastases;
- No prior bilateral orchiectomy;
- No active medical illness precluding treatment or limiting survival;
- No second malignancy within five years except adequately treated nonmelanomatous skin cancer, in situ bladder cancer or other superficial cancer; and
- No history of neurologic disorder, head trauma with loss of consciousness, learning disability, mental retardation, history of alcoholism, or psychosis.

Controls will be healthy men aged 50 and above with no history of: cancer chemotherapy; neurologic disorder; head trauma; learning disability, mental retardation, or other cognitive deficits; alcoholism; psychosis; or clinical depression at baseline. Because only adult men are affected by prostate cancer, women and children are excluded. English-speaking individuals from minority groups will be included in proportion to their representation in the clinical trial. The sample size is too small to permit meaningful ethnic comparisons.

Patient Accrual

We plan to recruit a total of 35 persons group, or a total of 105 participants. These will be recruited both locally and from other centers participating in the treatment protocol over a period of approximately two and a half years. We have requested funding for three full years.

Estimated Duration of the Study

We plan to complete this proposed study over a period of 36 months. Each subject will be asked to undergo a set of cognitive tests on three occasions, approximately three to four months apart, for approximately 90 minutes on each occasion. Thus each subject will participate for a total of 4 to 5 hours.

Participating Sites

The primary data collection site will be the University of Colorado Hospital in Denver. Other sites participating in the Phase III trial will also be used. At this time, Wayne State University is a definite participant, and the University of Arkansas may participate as well. The three most active SWOG, NCI, and ECOG sites have already enrolled a total of 253 patients, suggesting that we will have adequate numbers for the DoD study.

Data Collection Time Points

We will obtain baseline data on as many patients as possible. Since this is a supplement to a clinical trial, however, we may not have access to all patients before they begin CAD. However, the scientific literature on cognition and androgen levels strongly supports the assumption that adequate variation in androgen levels will occur for the intermittent CAD group between on- and off-treatment periods. Comparing androgen levels and cognitive functioning scores of the intermittent CAD group during the off-treatment period with the same variables for controls will provide an indication of whether CAD may have a lasting effect on cognition beyond the period of blockade. In addition, because we will have sex hormone levels at each time point for each subject, we will be able to ensure the equivalence of the hormonal milieu, which is fundamental to our comparisons. Should there be variability across groups in this regard, we will use the actual levels, as well as number of on-treatment periods undergone and duration of those periods as covariates.

Patients on intermittent CAD will be administered cognitive tests: 1) at baseline (before beginning CAD) if possible, or 12-16 weeks after discontinuation of androgen blockade; 2) 12-16 weeks following resumption of androgen blockade; and 3) 12-16 weeks after discontinuation of androgen blockade. Patients on continuous CAD also will be examined at three time points: 1) at baseline (before CAD) if possible or after at least 12 weeks on CAD; 2) after another 12-16 weeks of continuous CAD; and 3) after another 12-16 weeks of CAD. This design will allow comparison of the effect of CAD on cognition while controlling for practice effects. Control subjects also will be administered the tests on three occasions: 1) at baseline; 2) after 12-16 weeks; and 3) after another 12-16 weeks. According to Akakura et al. (1993), serum T returns to the normal range within a median of eight weeks (range 1-26 weeks) of stopping suppression, so waiting for three to four months after cessation of CAD, we can be fairly certain that serum T levels will be within normal limits for most participants even without assays (also see Nejat et al., 2000). Nevertheless, we will obtain T and estradiol assays at each time point. Because it will not be possible to obtain any off-treatment data for some continuous CAD patients, the crucial repeated measures comparisons for them versus the other two groups will be at time points 2 and 3.

Examination at each of the three time points will require about 90 minutes. To minimize fatigue, there will be a break midway through administration and more frequently if needed. For those unable to complete the testing in one sitting, they will be tested over two sessions. Data collectors will be trained to evaluate fatigue and asked to reschedule testing if fatigue appears to affect performance. To prevent unanticipated order effects in the cognitive assessment, the order of administration of tests will be randomized across subjects. To minimize circadian variability in performance (Blake, 1967), subjects will be scheduled for assessment at the time of day they prefer and these assignments will remain constant for each subject across time points.

Cognitive and Neuropsychologic Instruments to be Used

Following are the measures to be administered in this study, accompanied by brief discussion of their properties. Performance on certain of these tests has been shown to be dependent on level of T, of estrogen, or neither. Because T is converted into estradiol via aromatization, it is possible that cognitive effects observed as a result of T suppression could be a result of low levels of either of these hormones.

a. Working Memory: Working memory (Baddeley, 1990; short-term storage of information upon which cognitive operations simultaneously must be performed, or which is needed for performance of concurrent tasks) is often impaired among older adults (Raz, 2000). Among older men, working memory has been shown to be sensitive to T level (Janowsky et al., 2000). The following will be used as measures of working memory and immediate recall.

Letter Number Sequencing: A subtest of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler, 1997a) in which subjects are presented with mixed sequences of letters and numbers (e.g., 3-e-7-

9-p), then must separate letters and numbers and repeat them in the proper sequence (e.g., 3-7-9-e-p). The test is a reliable and valid measure of verbal auditory working memory (Wechsler, 1997a).

Visual Working Memory: This test involves recall of a set of abstract drawings presented in groups of 6, 8, 10, or 12, in different spatial arrangements on separate cards. Shown each card one at a time, the subject must touch a picture not previously touched in a series. An error occurs when the subject touches a card previously touched in that set (Petrides & Milner, 1982). This test was previously used by Janowsky and associates (2000) in their study showing that T affected working memory.

b. Speed and Capacity of Information Processing: Performance on most tasks is influenced by one's speed and capacity for processing information. Although these abilities have not typically been found to be associated with sex steroid levels (but see Asthana, et al., 1999c), they are sensitive to depression and fatigue. The following are considered direct measures of these abilities.

Symbol Digit Modalities Test (SDMT): This is a measure of processing speed (Smith, 1968). Similar to the Digit Symbol subtest of the WAIS-III, the subject is required to provide the number associated with each of nine different symbols. Scores are based on the number of correct responses in a 90-second trial. Reliability is very good. Performance on the SDMT has been shown to be associated with a number of neurologic conditions, and with the P3 component of evoked potentials (Spreen & Strauss, 1998).

Grammatical Reasoning: An experimental measure of simple reasoning sensitive to deficits in speed and capacity of information processing (Baddeley, 1968), it consists of 32 simple declarative statements having systematic variations in grammatical construction (e.g., "A is followed by B," "B is not preceded by A"). Each is followed by the letters **AB** or **BA**. The subject must say whether each statement about the letters is true or false. The subject's score is the number of items answered correctly in three minutes.

c. Declarative Verbal Learning and Memory: Among women and men, verbal learning and memory have been found to be sensitive to estrogen level. The influence of estrogen in men is less clear than in women, but performance on the following tests might well be influenced by absence of estradiol. It might also be influenced by deficits in working memory.

Logical Memory Subtest of the Wechsler Memory Scale-III (WMS-III): A test of declarative verbal memory, involving immediate and 30-minute delayed recall for two short paragraphs read to the subject by the examiner (Wechsler, 1997b). Interrater and test-retest reliabilities are > 0.90 (Wechsler, 1997b). We will use only one of the two paragraphs at each time point. For repeat testing, we will use the second paragraph and equivalent paragraphs from the second edition of the WMS (Wechsler Memory Scale-Revised).

Rey Auditory Verbal Learning Test (RAVLT): A brief, easily administered auditory verbal learning test comprised of 15 unrelated concrete nouns repeated for five trials. Recall is requested after each presentation of the words. After the fifth trial, a second interference list is read to the subject, and after a 20-minute delay, both recall and recognition are tested for the first list. The scores of interest are the number of words correctly recalled after the first presentation, the number recalled by the fifth trial, the number of words recalled after 20 minutes, and 20-minute recognition. Different, parallel forms of the test are available for retesting.

d. Verbal Reasoning: Verbal reasoning has not been shown to be affected by sex steroid levels. It may serve as an important covariate in analyzing data from other cognitive tests. These tests will be administered to provide an estimate of verbal intellectual level and to determine whether performance on them is influenced by T level.

Similarities and Vocabulary Subtests of the WAIS-III: The Similarities and Vocabulary subtests (Wechsler, 1997) will be used to assess general verbal reasoning ability. These are relatively independent of memory and are highly correlated with the Wechsler verbal IQ score. We anticipate little change in either score and intend to use these subtests primarily to control for verbal intelligence.

e. Verbal Fluency: Tests of verbal fluency have been shown to be sensitive to estrogen level in women. Whether, and to what extent, they are affected by sex steroids in men is unknown.

Controlled Oral Word Association Test (COWAT): Commonly described as a test of verbal fluency or cognitive flexibility, the COWAT reflects the ability to generate information actively and is correlated strongly with measures of executive functioning. Over three trials, the subject must say as many words as

he can think of in a 60-second period, starting with a given letter (F, A, and S). Reliabilities are very good to excellent (ranging from 0.70 to nearly 1.0; desRosiers & Kavanagh, 1987; Spreen & Benton, 1977).

f. Spatial Perception: Performance on tests of spatial perception has been found to be associated with T level. Among men, even relatively subtle variations in the level of this sex steroid may affect performance either positively or negatively. We will use the following tests.

Vandenberg and Kuse Mental Rotation Test: This consists of a number of line drawings of three-dimensional geometric objects (Vandenberg & Kuse, 1978). A stimulus figure is compared with four variations on this figure, one of which is identical to the stimulus figure except that it is drawn so it is rotated. The subject must select the identical rotated figure. This is the most commonly used test of mental rotation.

Benton Line Orientation Test: Two lines at different angles relative to the horizontal are presented on a card and the subject's task is to identify, on a second card, which of 12 different lines' angles match these. This test is a valid and reliable measure (Benton et al., 1983).

g. Depression: Depression and fatigue may affect performance on a number of the tests discussed above entirely independently of the influence of sex steroids or other factors. We, therefore, will collect data on these variables as covariates in the analysis. Depression will be evaluated using the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). This scale contains fewer items that might reflect physical disability than do other depression scales and has been demonstrated to be a reliable and valid measure of depression.

h. Quality of Life and Fatigue: Quality of life will be assessed using the SF-36, a general health status instrument used in the RAND Medical Outcomes Study (Ware & Sherbourne, 1992). The scale is reliable and valid as a measure of QOL (e.g., Andresen & Meyers, 2000; Lloyd et al., 2000). Scores on the fatigue subscale will be used to control for the effects of fatigue on performance. Subjects also will be asked to rate level of fatigue at each time point on a 10-point analog scale, noting current fatigue and average for the past week.

Laboratory Tests: Hormone Assays

Blood will be drawn in the morning, fasting within 1-2 days of the time a patient is examined to conduct assays for sex hormones. Because the free hormone level is the physiologically active component, we will obtain levels of total T, estrone, estradiol, sex hormone binding globulin (SHBG), and albumin to calculate free sex hormone levels. We propose that samples will be analyzed at the UCHSC General Clinical Research Center. This will permit us to ensure the equivalency of subjects' hormonal milieu and to adjust statistically for variability in sex steroid levels in the suppressed and non-suppressed states, to determine whether sex hormones may be the mechanistic explanation for cognitive differences due to CAD.

Training and Quality Control for Data Collection

Data collectors at each center will be responsible for enrolling subjects and administering all instruments. There will be one data collector at each participating site, which will mean a total of 4-6 data collectors. Most will be nurses who will be trained as follows. Data collectors will be trained face-to-face by one of the investigators in the administration of each test. Data collectors will then administer complete sets of the tests on three occasions to persons who are not study participants. At least two of these administrations will be observed directly, videotaped, or observed via videoconference. Differences or problems in administration and scoring will be discussed and reconciled between observers and data collectors. For each data collector, the first three actual assessments of participants will be observed by video as well, and feedback given to the data collectors. For the DoD-funded study, after each data collector has completed 10-12 patient exams, she or he will again be observed by the investigators. For the DoD protocol, we will conduct an interrater reliability analysis using 15 videotaped assessments of participants, and using the intraclass correlation coefficient (ICC). Videotapes will be destroyed on completion of the study.

Data Safety Monitoring Board

This project involves no treatment and entails negligible risk for participants. There consequently is no need for a Data Safety Monitoring Board. The probability of adverse events in association with this study

approaches zero. Because of the small sample involved, there will be no interim analyses, and study conduct will be monitored by the investigators using a simple subject tracking database.

Data Analysis

All data management and analysis will be conducted at the Center for Health Services Research (CHSR) of the UCHSC. Data will be double-entered to ensure quality control, with discrepancies resolved by review of original data forms. We will use SPSS and SAS for analysis.

To evaluate data integrity and completeness and to characterize the samples within each group, frequency distributions and descriptive statistics will be obtained. We then will assess mean differences among the groups on clinical and demographic factors. The overall analytic plan will include modeling cognitive functioning, using both mean differences (between continuous variables) and percent of persons classified as impaired (for dichotomous variables). Comparisons will be made over time and across the three patient cohorts included in this study. For continuous measures of cognition, repeated measures analysis of covariance (ANCOVA) and multivariate analysis of covariance (MANCOVA) will be used. An advantage of MANCOVA with the cognitive tests is that it limits the number of mean comparisons, hence avoiding inflation in experiment-wise Type I error rate. For example, MANCOVA might be used to examine working memory, with each test score as a dependent variable, treatment group as a fixed independent variable indicating on- or off-treatment status, and fatigue, depression, and T level as covariates. When multiple comparisons are made, we will use the Holm method (as opposed to those of Bonferroni or Dunn) of correction (Aickin & Gensler, 1996; Holm, 1979). For dichotomous measures, logistic regression models will be applied. We also will use multiple regression to assess the contribution of a number of different variables to specific dependent variables. Such variables as age, education, depression, comorbidity, verbal reasoning, and hormonal status may be included as covariates. In addition to these analyses, there are opportunities to profile patients at greatest risk of cognitive impairment (on variables such as age, education, comorbidity) using the approaches described above.

We conducted power analyses to assist in the determination of sample sizes. The projected sample size of 35 patients per group was determined by estimating statistical power ($1-\beta$), then adding to the total in order to deal with possible problems resulting from attrition. We anticipate adequate power to detect small-to-moderate differences over time, as well as among the three groups. We estimated necessary sample sizes to obtain power using repeated measures analysis of variance (ANOVA) with three conditions and a total of three measures per subject. Based on cognitive research in other contexts, we assumed an effect size of 0.4, which is about midway between what Cohen (1977) considered small (0.25) and medium (0.5) effect sizes. With this effect size, at $\alpha = 0.05$, 22 subjects are required to achieve power $(1-\beta) = 0.80$. At $\alpha = 0.01$, it would require 31 subjects to achieve $1-\beta = 0.80$.

Risks: Subjects, Investigators, and Institutions

There are no physical risks entailed in this cognitive study. Participants will be interviewed, and will be asked to perform a set of tasks that pose no physical danger to them. There are no invasive medical procedures in this study other than a simple venipuncture which may result in transient discomfort and possible bruising. If a participant states that he is physically unable to perform such a task, he will not be asked to do so. Data collectors will monitor subjects closely to ensure that no harm comes to any participant, and will attempt to put participants at ease throughout the interview. A rest break will be provided midway through the interview, and other short breaks will be encouraged should subjects become anxious or fatigued. Sensitive information, such as that relating to child abuse, drug use, or reportable infectious diseases, will not be obtained. There are no known risks to either the investigators or to the institution. To protect subject confidentiality, each participant will be assigned a numeric identifier. These ID numbers and personal identifiers will be kept separate, and all records will be kept in locked cabinets. Computerized databases will be password-protected, and after data collection is completed for a subject, identifying data fields for that subject will be deleted. Data will be presented only in aggregate form, with no identifying subject information. Only authorized study personnel will have access to subject data.

There are no risks to either investigators or institutions participating in this study. However, adverse experiences that are both serious and unexpected will be immediately reported by telephone to the USAMRMC Deputy Chief of Staff for Regulatory Compliance and Quality (301-619-2165) (non-duty hours call 301-619-2165 **and** send information by facsimile to 301-619-7803). A written report will follow the initial telephone call within 3 working days. Address the written report to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

Benefits

There are no direct benefits to any subject that may reasonably be expected from the research. There is no monetary compensation. The scientific benefit of the study is a greater understanding of the possible effects of CAD on cognitive functioning among men with prostate cancer, and specifically of the influence of sex steroids on cognition. The informed consent form indicates that subjects should expect no benefits of any type from participation in the study.

Funding

The larger protocol of which the current proposal is a sub-study is funded by the National Cancer Institute. We have applied for funding from the Department of Defense for this ancillary study of quality of life. That application is pending, and the Department of Defense has requested COMIRB review before further action is taken on funding recommendations.

Modification of the Protocol

Any change(s) made to the protocol and consent form must be submitted to the local IRB and to the Human Subjects Research Review Board (HSRRB) for review and approval before implementation.

Responsibilities of Study Personnel

Jim Grigsby, PhD: Dr. Grigsby will be Principal Investigator, with overall responsibility for all aspects of the proposed research study. He will coordinate communication among the participating facilities and the research team, assist in recruitment and training of data collectors, monitor subject recruitment, and supervise all project staff. He will be involved in specification and conduct of data analyses and will have lead responsibility for preparation of interim and final reports, as well as journal articles and abstracts presented at research meetings.

Mike Glodé, MD: Dr. Glodé is a Professor of Medical Oncology at UCHSC and is the local PI for SWOG protocol 9346. As a Co-Investigator, he will play a primary role in subject recruitment, oversee the clinical status of all local participants, and communicate with other participating collaborative group study sites. He will be senior medical consultant to the research team, and will be involved in specification of data analyses and preparation of abstracts and journal articles.

Angela Brega, PhD: Dr. Brega is a Co-Investigator on the proposed study. A research scientist at CHSR, she has extensive experience as a project manager on a number of large-scale national studies. Dr. Brega will supervise the training and ongoing monitoring of data collectors and of establishment of a system for data management and quality assurance. She will be involved in specification and conduct of data analyses and will be very involved in preparation of interim and final reports, as well as abstracts and journal articles.

Peter Shaughnessy, PhD: Dr. Shaughnessy is a mathematical statistician, health services researcher, and Director of CHSR. He will serve as a Co-investigator. He has been involved in the design of the research and will play a major role in specification of data analyses, in oversight of data analyses, and in preparation of abstracts and journal articles.

Glenn Goodrich, MS: Mr. Goodrich, the primary study Data Analyst, will be involved with the setting up of a database during year 01, and with conducting analyses specified by the PI and Co-Investigators during year 02 (preliminary descriptive analyses) and year 03 (descriptive and final analyses).

Patricia DeVore, BS: Ms. DeVore, a Research Assistant and the Study Manager, will be involved in management of operational details of the project, communication with subjects and other data collectors, and

scheduling. It will be her responsibility to collect data locally and this individual will be trained sufficiently to be able to provide technical support for data collectors at other sites.

Administrative/Clerical Support: This individual will be responsible for data entry and checking, as well as for provision of all administrative support services as needed by the project staff. The percentage of time for which this individual will be assigned to the project was determined on the basis of past experience at CHSR on projects of a similar nature, estimated as a percentage of research staff participation.

Sanjay Asthana, MD is a consultant to the study. He is a geriatrician and Associate Professor of Medicine at the University of Washington School of Medicine and a staff physician at the GRECC at the VA Puget Sound Health Care System. Dr. Asthana has considerable experience in the effects of sex steroids on cognitive functioning, and will provide expertise in this area to the research team. Dr. Asthana will participate in specification of data analyses, and in the preparation of all reports and publications from this project.

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