Evidenced-Based Practice in Wound Care
September 15-16, 2006
Cleveland, Ohio

Problems Encountered and Lessons Learned

Anabolic Steroid Therapy on Pressure Ulcer Healing in Persons with Spinal Cord Injury (CS #535)

William A. Bauman, M.D.

Chairman, VA Cooperative Study

Professor of Medicine & Rehabilitation Medicine
Mount Sinai School of Medicine, New York, NY

Problem 1:
What is the appropriate funding agency?

Government
- DVA
- NIH (NCI, etc.)
- Dept of Ed (NIDRR)

Industry
- Pharmaceutical
- Device Company

Private Foundation

Considerations
- Study population
- Size of study
- Location(s)
- Intervention

Department of Veterans Affairs (DVA)

Cooperative Studies Program
permits PIs to answer certain questions with randomized clinical trials.

The infrastructure provided for the investigator/study is amazing!

Study Data Management

VA Cooperative Study Program Coordinating Center

- Director
- Biostatistician
- Project manager
- Statistical programmer
- Database programmer
- Two computer assistants

Will provide:

- Pharmacy support
- Administrative support
- Data processing
- Statistical support

Sequence of Events for VA Cooperative Study

Letter of Intent	February 2001
Coordinating Center (CSPCC)	December 2001
Clinical Research Pharmacy Coordinating Center (CRPCC)	December 2001
First Planning Committee	April 2002
Second Planning Meetings	June 2002
Proposal Submission	August 1, 2002
Cooperative Studies Scientific Merit Review Board (CSSMRB)	October 3, 2002
Response from CSSMRB	November 2002
Feasibility Planning Meeting	January 9-10, 2003
Kickoff Meeting	June 20-22, 2003
Annual Meeting	May 11-12, 2004
Feasibility Study Final Report	September 2004
Response to Feasibility Reviewers	December 1, 2004

The “Idea”

-- Original
-- Important (“must” be done)
-- Not being done
-- Sufficient preliminary work to justify the study

Problem 2:
How do you choose the objective?

New (not too new: a natural outgrowth of prior work)
Exciting (clinically and intellectually)
Scientifically Sound
Economically Feasible
Doable

Problem 3:
How best to write the proposal?

There is a structure and cohesion to a fundable grant.

- **It must follow the grant agency's interests & guidelines.**
- **It must read well.**
- **It must look "good".**

Components of a Study

- Interventions/Treatments/Services to be compared
- Population to be studied
- Sampling strategy (Where are you going to get patients?)
- Data collection methods (who, where, when, how)
- Research design (interventional or observational study)
- Endpoints to be evaluated
- Logical links between questions, data, & endpoints
- Duration of study
- Number of subjects
- Participating medical centers
- Resources (personnel and total cost)

Problem 4:
Who do you choose to assist in designing the study?

Make a "wish list" of individuals

- **In house and out-of-house**
- **Cover all the "specialties of interest"**
- **Try to bring in a diversity of opinion**

Go get them!!

Study Planning Committee

- Committee Members
  - Physicians
    - Internists
    - Physiatrists
    - Surgeons
    - Psychiatrist
  - Physiologist
  - Dietician
  - Industry Representative(s)
  - “Niche” Members
    - (Economist, Biostatistician,
    - Pharmacist, Molecular Biologist, etc.)
  - Administrators

Composition of the VA Cooperative Study Planning Committee

- Principal Proponent
- Expertise in Fields of Study
- Clinical Research Pharmacy
- 2 Potential Site Investigators
- Expert in Economic Analysis
- Study Biostatistician(s)
- Administrative Personnel

Planning Committee: Areas of "Heated" Discussion

- Do we need a Screening Phase?
- Length of Screening Phase or Treatment Phase?
- Inpatient vs. outpatient study?
- Standards of care?
- Definition of osteomyelitis?
- Follow a single pressure ulcer or all wounds?
- Adjuvent therapy?
- Definition of a "healing" wound?
- Definition of a "healed" wound?
- Inclusion/Exclusion criteria?
- Measurement tool?
- Mobilization protocol?

Problem 5:

What is the best tool to assess pressure ulcer size and characteristics?

Desired Attributes of the Tool:

- Accurate
- Reproducible
- Sensitive
- Standardized

Assessment of Pressure Ulcer Size

Area

- Length x Width
- Overlaying the wound circumscribing its outline:
  - cutting & counting graph paper
  - cutting & weighing transparent film
- Planimetry Techniques
- Digital Image

Volume

- Manual measurements
- Saline instillation
- Gel molds
- Stereophotographic digitized measurements

VeV MD - Measurement Documentation

Patients Wounds Records Image Tracking Filter Data Tools Printing Help

Select Patient: Sample, Joe js1 | Mark | Select Wound: April 03, 1997 Pressure Left Ischium | Ma

Wound Record: | Mark

07/07/97 W
06/06/97 W
05/30/97 W
05/23/97 W
05/09/97 W
04/30/97 W Pr
04/24/97 W
04/17/97 W
04/03/97 W Pr N P E

Dates | Thumb Nails

Capture New Image

Load New Image

Add Record | Tracking

Wound Description | Image | Patient Info. | Patient Assessment

Location: Left Ischium
Etiology: Pressure
Type: Stage IV
Orientation: Left

Description Comments:
- Granulation tissue evident
- Tunneling noted at 10 o'clock
- Serous drainage

Outline for Measurements:
Area

Area:	19.28	cm^2
Length:	6.43	cm
Width:	4.82	cm
Perimeter:	18.58	cm
Area/Perim:	1.04	cm
Depth:	0.00	cm
Volume:	0.00	cm^3

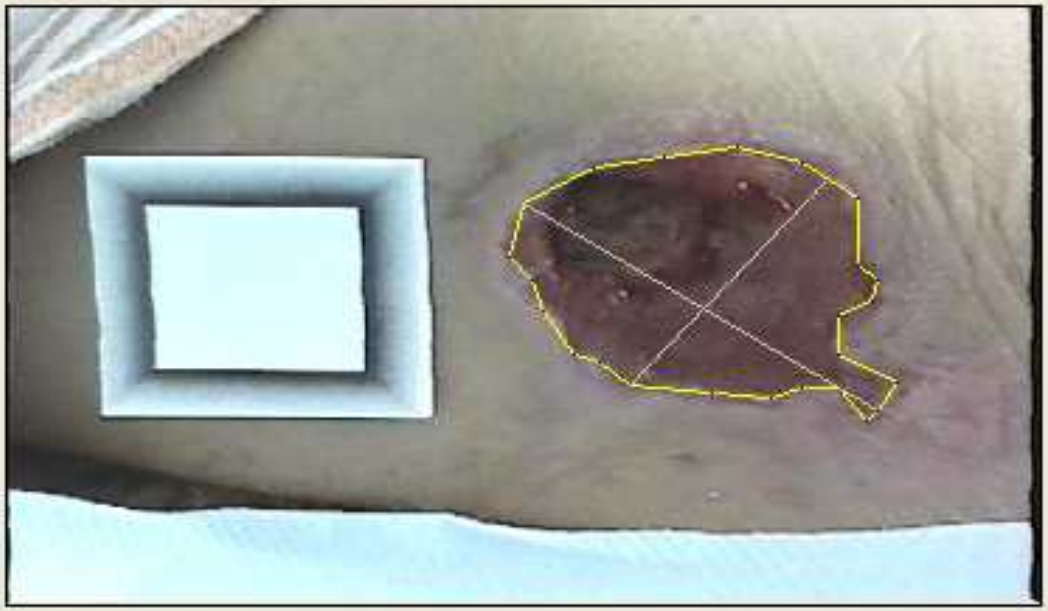
Hue: 0.523

	Primary:	Secondary:
Color:	Red	
Drainage:	Small - Serous	None
Tissue:	Granulation	Muscle
Assess:	Moderate Improvemer	
Edge:	Open	
Sympts.:	None	
Odor:	None	

Pain Status
Pain | Pain Resolution

Surrounding Ski
Erythematous
Warm
Indurated
Mottled
Bruised
Macerated
Rash
Calloused
Blanchable

Tunnelling
Undermining



Problem 6:

Is it possible to keep vested interests from potentially undermining the study?

The study must be as scientifically sound as possible.

VA Cooperative Study

Threat to our CS study: Adjunctive Therapies

The PI and planning committee Members argued against the use of adjunctive therapies during the drug intervention.

Advice for PI for the Planning Stage

Go in with an open mind.

Know how to close your mind.

Problem 7:

How do you stress the importance of the study?

Clinical Benefit

Scientific Value

Economic Savings

Political Attractiveness

Point of Reference

Everyone's work is the most important in the universe.

You have to convince others of its significance: sell, sell, sell!

The soft sell.

Prevalence and Expense: SCI Care in the Department of Veterans Affairs

For Fiscal Year 2000:

Primary Diagnosis of Pressure Ulcers

SCI Service Inpatient Days: 23% of total
Cost: $130 million

Primary and/or Secondary Diagnosis of Pressure Ulcers

SCI Service Inpatient Days: 41% of total
Cost: $247.8 million (50% of SCI care)

Hendricks, RD, Health Systems Specialist, NSCI, Personal Communication

Other Conditions with Immobilization and Pressure Ulcers

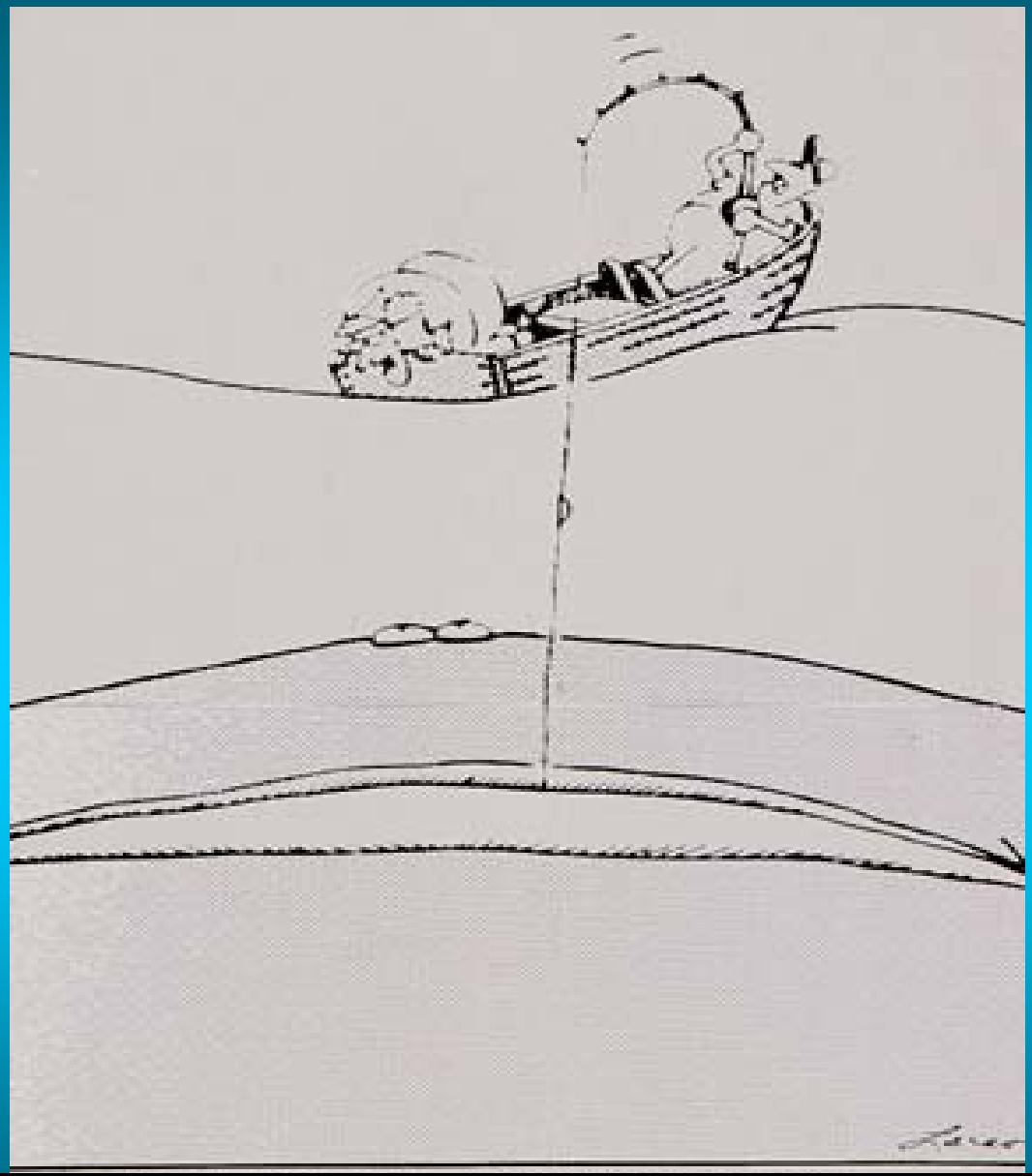
- Frail elderly
- Stroke & degenerative neuromuscular diseases
- Traumatic brain injury
- Lower extremity amputation
- Rheumatological diseases
- End-stage cardiopulmonary disease

Economic Implications of Pressure Ulcers
(Extrapolation from existing information)

- Hospitalized patients alone are estimated to exhibit an annual prevalence of 2.5 million pressure ulcers.
- The cost has been estimated to be between $2.2 to 3.6 billion annually.
- The annual cost nationwide related to pressure ulcer treatment in hospitals, nursing homes, and home care has been reported to be upwards of 5 to 8 billion dollars.

Beckrich K, et al. *Nurs Economics* 1999;17;263-371.

Miller H, et al. Cost implications. In: Treating pressure Ulcers: Guideline Technical Report, Vol. II, No. 15, 1994. Publication 96-N015.



“Good heavens Stuart! We’re going to need the net.”

Problem 8:
Should you get the proposal pre-reviewed?

Pick your reviewers carefully
Allow them time to review the proposal
Allow yourself time to make the changes

Problem 9:
Who should provide letters of support?

Local (Administrative)
Collaborators
National Experts
Industry

Problem 10:

How do you choose the investigators & the sites?

(Not necessarily in that order)

- Need the “numbers”—that is, eligible subjects
- Investigators must be able to work well together
- Collaborators should be dedicated to the project
- Site must be organized and “competent”

VA Cooperative Study:
A Couple of Problems Right Out of the Starting Gate

» At start-up, the continuing resolution made purchasing equipment & hiring staff difficult.

» A couple of the potentially “best sites” did not have site principal investigators.

"I was wondering when you'd notice there's lots more steps."

Full Protocol Overview

I. Screening Phase

- Study site provides best effort to heal the pelvic pressure ulcer during the 28 days of observation

II. Treatment Phase (drug or placebo)

- If ≤15% closure during Screening Phase, subject is eligible for participation in Treatment Phase
- Expected to enroll 400 patients over 5 years
- Inpt care until pressure ulcer is healed or 24 wks
- F/U 4 and 8 weeks after pressure ulcer healing

Treatment Phase: Primary Objective for (CS #535)

To determine whether SCI inpatients with a Stage III or IV pressure ulcer of the pelvic region who receive 24 weeks or less of optimized clinical care (i.e., guideline-driven care with nutritional support) and an oral anabolic steroid agent (oxandrolone) have a greater percent of healed target pressure ulcers than those who received placebo and the same clinical care.

VA Cooperative Study: Primary Outcome Measure

The primary outcome measure is a healed pressure ulcer, defined as re-epithelialization to a cicatrix with a dry surface and zero open area for a minimum of 96 hours (4 days).

Number of "Expected" Pressure Ulcers to Heal*

Patients on placebo	50 of 200 healed (25%)
Patients on oxandrolone	80 of 200 healed (40%)

*Healing rates determined by nominal group technique

VA Cooperative Study: Power Calculation

- The study can attain power of:

- 80% with 304 patients

- 85% with 346 patients [loss of up to 13.5% (54 patients)]

- 90% (0.8966) with 406 patients

Major Secondary Objective

To determine whether a healed pressure ulcer remains closed at 8 wks.

Number of Healed Pressure Ulcers "Expected" to Remain Closed at 8 weeks*

25 of 50 (50%) patients on placebo

60 of 80 (75%) patients on oxandrolone

*Numbers determined by nominal group technique

Other Secondary Objectives

1. To compare the number of patients who demonstrate a pressure ulcer healing rate of >15% closure during the 4 weeks of the Treatment Phase.

2. To determine whether oxandrolone therapy improves general nutritional status.

   Biochemical Markers (Albumin and Prealbumin)
   Caloric and Protein Intake
   Body weight
   Nutrition Status Classification (VA Form 10-0364)

Other Secondary Objectives

3. To evaluate the effects of oxandrolone therapy on the inflammatory response.

4. To evaluate the effect of oxandrolone therapy on plasma insulin-like growth factor-1 (IGF-1).

5. To compare the economic impact in the two treatment groups (oxandrolone vs. placebo)

Problem 11:
How does the PI motivate study investigators?

As Principal Investigator, it works to your benefit to be a "credible and well liked entity" and the work must be perceived as important to the site investigators when you persuade them to participate.

Problem 12:

How do you deal with inexperienced investigators?

- » Provide adequate training
- » Assist during the IRB submission process
- » Reinforce need to follow study protocol
- » Record/report deviations from protocol
- » Advise on hiring study personnel

Submission to Local IRBs

Extremely Labor Intensive Process

» Each IRB is different.

» Must maintain study integrity.

» PI must be available.

VA Cooperative Study

The SCI Services have never been harnessed by the Cooperative Studies Program to address research questions.

Proposed 15 Sites:

VA Medical Center SCI Services

Augusta, GA
Bronx, NY
Cleveland, OH
Dallas, TX
Hines, IL
Houston, TX
Long Beach, CA
Miami, FL
Milwaukee, WI
Palo Alto, CA
Richmond, VA
San Diego, CA
St. Louis, MO
Tampa, FL
West Roxbury, MA

Problem 13:

How do you satisfy the concerns of the granting agency?

Do not get upset (or angry)!!!!
Respond honestly and directly.
Make every effort to make the response complete.
Additional information may be needed that will require additional preliminary work.

Specific Concerns of the Cooperative Studies Scientific Merit Review Board

Requiring Additional Preliminary Investigation

- Determine actual rates of patient accrual/refusal.
- Determine intra- and inter-rater reliability of the wound measurement approach proposed.
- Determine whether a full-time SC is required.

Able to Address without Additional Studies

- Determine approaches for standardizing the nutritional component of the intervention.
- Reduce the number of outcome measures.
- Re-examine the utility of the economic analysis.

Option: Feasibility Study

VA Cooperative Study

Feasibility Study Planning Committee

Feasibility Study Protocol:

12 sites for Screening only

2 sites: Full Study (Screening & Treatment)

Submission of Feasibility Proposal

Information Obtained During the VA Feasibility Study

1. The number of Stage III and Stage IV pressure ulcers eligible for in the Treatment Phase.
2. The intra- and inter-rater reliability of the wound measurement approach was determined.
3. Documented that a full-time site coordinator is required to perform the Treatment Phase.

Problem 14:
How do you enroll sufficient study subjects?

Design a doable study!

- » Review the inclusion/exclusion criteria
- » Constant communication with study personnel
- » Hire top-notch study personnel
- » Monitor the “losses” to enrollment

Enrollment Problems Persist & Threaten the Study

If all else fails:

» Consider protocol changes

VA Cooperative Study: Patient Accrual

To achieve an enrollment in the Treatment Phase of 400 patients over a 4-year period, each of the 15 sites would be expected to recruit 6-7 patients/yr.

VA Cooperative Study:
Keeping in Touch with Study Sites

Chairman's Office

Chairman

Co-Chairman

National Coordinator

CSP Coordinating Center

Project Manager

Director

VA Cooperative Study:
Keeping in Touch with Study Sites

Monthly conference calls

Email correspondence:
group and individual

Newsletter

Yearly Meetings

VA Cooperative Study: Budgets

Feasibility Study:

- $1.5 million for 1 year

Full Study:

- $ 12 million for 5 years (direct)
- $12 million for 5 years (indirect)
- $84 million (inpatient stay)

VA Cooperative Study: Bumps Along the Road

» Finding and retaining SCs and SIs.

» Obtaining drug/placebo from industry.

» One of our Full Study sites was not sufficiently productive and had to be replaced.

» National Coordinator was replaced.

» Waiting for Full Study funding after completing the Feasibility Study.

» Discharge of patients/subjects who wish to continue in the study.

What the study will accomplish…

Healing Issues:

- Percent healed
- Healing rate
- Nutritional factors
- Endocrine/metabolic factors
- Immunological factors
- Drug intervention

Economic Considerations:

- Total costs of pressure ulcer care
- Net cost savings of the intervention
- Quality Adjusted Life-Year (QALY)

Off to the Races!