

UNITED STATES OF AMERICA

+ + + + +

FOOD AND DRUG ADMINISTRATION

+ + + + +

CENTER FOR DRUG EVALUATION AND RESEARCH

+ + + + +

DERMATOLOGIC AND OPHTHALMIC DRUGS  
ADVISORY COMMITTEE

+ + + + +

46TH MEETING

+ + + + +

TUESDAY,  
JULY 15, 1997

+ + + + +

BETHESDA, MARYLAND

The Advisory Committee met in the Versailles Room of the Holiday Inn, 8120 Wisconsin Avenue, at 8:30 a.m., Joseph McGuire, Jr., M.D., Chairman, presiding.

PRESENT :

JOSEPH McGUIRE, JR., M.D.  
KEN HASHIMOTO, M.D.  
EDUARDO TSCHEN, M.D.  
SUSAN COHEN, B.S.  
JOEL MINDEL, M.D.  
E. WILLIAM ROSENBERG  
M. ROY WILSON, M.D.  
LYNN M. DRAKE, M.D.  
TRACY RILEY, Executive Secretary

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

SPECIAL GOVERNMENT EMPLOYEES, CONSULTANTS, AND GUESTS  
PRESENT :

WILMA F. BERGFELD, M.D.  
O. FRED MILLER, III, M.D.  
EVA F. SIMMONS-O'BRIEN, M.D.  
PHILIP T. LAVIN, Ph.D.  
LAWRENCE B. HARKLESS, D.P.M.  
BENJAMIN A. LIPSKY, M.D.  
DAVID J. MARGOLIS, M.D.  
CLINTON M. MILLER, III, Ph.D.  
THOMAS A. MUSTOE, M.D., Ph.D.  
DAVID R. THOMAS, M.D.  
DIANE COOPER, Ph.D., R.N.

Also Present :

Kurt Stromberg, M.D.  
Karen Weiss, M.D.  
Liberio Marzella, M.D., Ph.D.  
David Finbloom, M.D.  
William H. Eaglstein, M.D.  
Celia Witten, Ph.D., M.D.  
Joanne Less, Ph.D.  
Jonathan Wilkin  
Kathryn O'Connell, M.D., Ph.D.  
Ellen Redding  
Ruth Bryant  
Adrian Barbul  
George Cherry  
Oscar Alvarez  
Diane Krassner  
Stephen L. Harlin, M.D.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

	3
A-G-E-N-D-A	
Introduction, Chairman McGuire	4
Conflict of Interest Statement	8
Public Comment Session	
Advanced Tissue Sciences, Ellen Redding	9
Wound Ostomy and Continence Nurses Society, Ruth Bryant	15
Discussion Objectives, Karen Weiss	20
TOPIC 1: STANDARD OF CARE	
Variability of wound management	26
Aspects of wound care	52
Methods for compression load pressure management	63
Perforator competence and Doppler studies	68
Debridement of venous stasis ulcers	78
Dressings	90
Surgical closure	94
Systemic antimicrobials	96
TOPIC 2: DISCONTINUATION OF STUDY TREATMENT FOR ADVERSE EFFECTS, BLINDING, AND VEHICLE CONTROLS	
Impacts of infection and removal from trial	107
Third party evaluation	130
Vehicle controlled studies	138
TOPIC 5: ENDPOINTS	
Ulcer closure	155
Products defined by the sponsor as wound healing agents	164
Ulcer recurrence	195
Wound debriding agents	201
Wound deodorizing agents, topical a n t i m i c r o b i a l           a n d topical analgesics	211
Acceptable closure	219
TOPIC 3: ENTRY CRITERIA INDICATIONS	251
TOPIC 4: WOUND ASSESSMENT	270
TOPICE 6: STERILITY OF THE PRODUCT	299

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

P-R-O-C-E-E-D-I-N-G-S

(8:38 a.m.)

CHAIRMAN MCGUIRE: Good mornin g. This is the day 2 of the 46th meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee meeting.

The meeting today will be structured quite differently than the meeting yesterday. We're doing something that's different, a little bit different, for this committee, and also it's a little bit different for the agency. The agency is generating a guidance document for wound care and wound care products, and it is their purpose that we help them and advise them in assembling this.

We have some different people at the table this morning. We still have a pretty big table so I'd like to start at my right and have members of the advisory committee and the FDA introduce themselves, beginning with Doctor Wilkin.

Could we have some sound. Sir, if you could just stay over there for a while, we're going to introduce the people at the table.

Doctor Wilkin.

DOCTOR WILKIN: Jonathan Wilkin, Director, Division of Dermatologic and Dental Drug Products.

DOCTOR LESS: Joanne Less, Director of the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Investigation Device Exemption staff.

2 DOCTOR WITTEN: Celia Witten, Division  
3 Director for the Division of General and Restorative  
4 Devices in the Office of Device Evaluation.

5 DOCTOR WEISS: Karen Weiss, the Director  
6 of the Division of Clinical Trials in the Center for  
7 Biologics.

8 DOCTOR MARZELLA: Louis Marzella, reviewer  
9 in the Division of Clinical Trials.

10 DOCTOR THOMAS: David Thomas, Geriatric  
11 Medicine.

12 DOCTOR HASHIMOTO: Ken Hashimoto,  
13 Department of Dermatology, Wayne State University in  
14 Detroit.

15 DOCTOR MUSTOE: Thomas Mustoe, Division of  
16 Plastic Surgery, Northwestern University in Chicago.

17 DOCTOR FRED MILLER: Fred Miller,  
18 dermatologist, Geisinger Division of the Penn State-  
19 Geisinger Health System.

20 DOCTOR DRAKE: Lynn Drake, Department of  
21 Dermatology, University of Oklahoma Health Science  
22 Center.

23 MS. RILEY: Tracy Riley, Executive  
24 Secretary to the committee.

25 CHAIRMAN MCGUIRE: Joseph McGuire,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Pediatrics and Dermatology, Stanford, California.

2 DOCTOR BERGFELD: Wilma Bergfeld ,  
3 Departments of Dermatology and Pathology, The  
4 Cleveland Clinic Foundation.

5 DOCTOR MINDEL: Joel Mindel, Departments  
6 of Ophthalmology and Pharmacology, Mount Sinai Medical  
7 Center, New York.

8 DOCTOR SIMMONS-O'BRIEN: Eva Simmons -  
9 O'Brien, Departments of Dermatology and Internal  
10 Medicine, Johns Hopkins University Hospital.

11 DOCTOR ROSENBERG: Bill Rosenberg ,  
12 Dermatology at the University of Tennessee, College of  
13 Medicine.

14 DOCTOR COOPER: Diane Cooper, Colleges of  
15 Nursing and Medicine, University of South Florida, and  
16 Institute for Tissue Regeneration, Repair, and  
17 Rehabilitation in Bay Pines, Florida.

18 DOCTOR TSCHEN: Eduardo Tschen, Department  
19 of Dermatology, University of New Mexico.

20 DOCTOR LAVIN: Phil Lavin, Boston  
21 Biostatistics and Harvard Medical School.

22 MS. COHEN: I'm Susan Cohen, I guess I can  
23 say Boston, too. And I co-host and produce a radio  
24 program on consumer issues.

25 DOCTOR MARGOLIS: David Margolis ,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Department of Dermatology and Department of  
2 Biostatistics and Epidemiology, University of  
3 Pennsylvania School of Medicine.

4 DOCTOR HARKLESS: Larry Harkless ,  
5 podiatrist, Department of Orthopedics, University of  
6 Texas Health Sciences Center, San Antonio.

7 DOCTOR LIPSKY: Benjamin Lipsky ,  
8 University of Washington, general internal medicine  
9 and infectious diseases in the VA Puget Sound.

10 DOCTOR WILSON: M. Roy Wilson ,  
11 ophthalmology, Charles Drew University and UCLA.

12 DOCTOR CLINTON MILLER: Clint Miller ,  
13 Professor Emeritus, Medical University of South  
14 Carolina.

15 CHAIRMAN MCGUIRE: Thanks very much.

16 Tracy Riley, the Executive Secretary, will  
17 a conflict -- Oh, sorry.

18 DOCTOR O'CONNELL: Kathryn O'Connell ,  
19 Division of Dermatology and Dental Drug Products, FDA .

20 CHAIRMAN MCGUIRE: You've got to be on  
21 time.

22 Doctor -- Tracy Riley will read the  
23 conflict of interest statement.

24 MS. RILEY: Thank you. Good morning.

25 This is the conflict of interest statement

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 for the Dermatologic and Ophthalmic Drugs Advisor y  
2 Committee for July 15th.

3 The following announcement addresses the  
4 issue of conflict of interest with regard to thi s  
5 meeting and is made a part of the record to preclude  
6 even the appearance of such at this meeting. Based o n  
7 the submitted agenda for the meeting and all financia l  
8 interests reported by the committee participants, it  
9 has been determined that since the issues to b e  
10 discussed by the committee will not have a uniqu e  
11 impact on any particular firm or product, but rather  
12 may have widespread implications to all simila r  
13 products, in according with 18 U.S. Code 208(b)(3) ,  
14 general matters waivers have b een granted for today's  
15 meeting.

16 In the event that the discussi on involves  
17 any other products or firms no t already ont he agenda  
18 for which an FDA participant has a financial interest ,  
19 the participants are aware of the need to exclud e  
20 themselves from such involvement and their exclusion  
21 will be noted for the record. With respect to al l  
22 participants, we ask in the in terest of fairness that  
23 they address any current or previous financia l  
24 involvement with any firm whose products they may wish  
25 to comment upon.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 CHAIRMAN MCGUIRE: I think we have  
2 speakers for the public session.

3 Is there anyone here from Advanced Tissue  
4 Sciences? This is Ellen Redding.

5 MS. REDDING: Good morning. My name is  
6 Ellen Redding. I'm the Vice President of Regulatory  
7 Affairs and Quality Systems for Advanced Tissue  
8 Sciences. I welcome the opportunity to work with FDA  
9 and with the advisory panel on what I believe is a  
10 very important topic of discussion, certainly very  
11 timely in this day and age when we are appreciating  
12 more fully the importance of conducting chronic wound  
13 studies with some novel therapies as well as some  
14 unique opportunities for this patient population. I  
15 think this is, as I said, a very timely discussion and  
16 guidelines for future studies would be greatly  
17 welcomed.

18 Advanced Tissue Sciences has been involved  
19 in chronic wound studies for many years now in the  
20 field of tissue engineering which has allowed us some  
21 very unique opportunities to work with some unique and  
22 potentially innovative products in this area. We have  
23 worked in the area of venous stasis ulcers, pressure  
24 ulcers, and now diabetic foot ulcers.

25 So, we welcome the opportunity to provide

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 some suggestions, some experiences that we've had, and  
2 hopefully what will be a very fruitful discussion this  
3 morning and will lead to some guidelines that the  
4 entire industry and the entire field of medicine can  
5 appreciate over time.

6 Certainly we believe that pivotal chronic  
7 wound healing studies should and can be very well  
8 controlled. This is an area where industry is  
9 becoming increasingly more involved. These are very  
10 large, very expensive trials. There is a great deal  
11 of competition for this patient population base and in  
12 many, many -- at many, many times, it is very  
13 difficult to know whether or not we have a successful  
14 therapy until the termination of a very large, very  
15 expensive trial. So, we need to take every  
16 opportunity that we can to be creative, to reduce  
17 costs as much as possible. Ultimately to reduce costs  
18 of the therapies to the population.

19 Unlike active acute wounds, chronic wounds  
20 are typically secondary by-products of the underlying  
21 disease which offers many, or provides many, variables  
22 to these clinic settings. And in order to control as  
23 many of these variables as possible and limit the size  
24 of the trial, I think we need to be very sensitive  
25 to the patient population that we're dealing with.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           In the cases where there are gold  
2 standards of care, standard therapies which do exist,  
3 I think we need to pay particular attention to these.  
4 It is very important, very valuable pieces of  
5 information upon which we can design very solid clinical  
6 trials. In the case where there are solid and  
7 building historic controls, this information can  
8 provide us a great deal of insight into the standard  
9 adverse reactions expected in this patient population,  
10 for instance, or certainly the availability of typical  
11 standards of care to this patient population for  
12 control purposes. When there are cases where there is  
13 not agreement on what a standard of care may exist,  
14 then you do have more opportunities for creativity.  
15 But certainly where there are large and increasing  
16 patient populations, we do have an opportunity to  
17 reduce our sample size, perhaps, and look at the  
18 possibility of a 2 to 1 or a 3 to 1 clinical study  
19 design.

20           Increasing availabilities of incentive  
21 therapies do not always lend themselves to the more  
22 desirable double blind studies. In the case of tissue  
23 engineered products, for instance, and when we're  
24 dealing with tissues such as Dermagraft, a product is  
25 frozen and must be thawed at the patient's bedside or

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 in the clinic. And these kinds of situations do not  
2 lend themselves to double blind studies.

3 The study design must insure that the  
4 effectiveness of the treatment can be determined. We  
5 need to absolutely be able to tell at the end of the  
6 study that our treatment had in fact made the  
7 difference. And to that end, the control arm needs  
8 to be very carefully developed. Both the control arm  
9 and the treatment arm to the extent possible, should  
10 receive the same treatments so that at the end of the  
11 study we certainly can tell that the treatment that is  
12 being studied is the one that is making the  
13 difference.

14 We have to take into consideration the  
15 issues of practicality in the compliance when you're  
16 dealing with design of a control arm or the standard  
17 of care. And we must allow the patients to continue  
18 an active way of life.

19 Control of all the variables or as many  
20 variables as possible is certainly desirable but  
21 flexibility is required. You cannot always measure  
22 the compliance of the patients. When you're dealing  
23 with issues such as weight bearing or the possibility  
24 that bed rest may be the optimal method of healing of  
25 certain ulcer types, you should always try to take

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 into consideration what the patient will or will not  
2 bear, what the patient population expects or cannot  
3 comply with. Certainly we have heard that in certain  
4 cases bed rest is the optimal method of treating  
5 certain types of ulcers but when you're dealing with  
6 a patient population that may include patients in the  
7 work force or may include individuals who are primary  
8 care givers, this is not a practical source of a  
9 healing methodology. So, this needs to be taken into  
10 account in the patient population that you're dealing  
11 with.

12           And of course, objective endpoints need to  
13 be established for complete healing but we need to  
14 avoid, whenever possible, the need for a third party  
15 blinded assessment. This is not always practical in  
16 the clinical setting and it also adds to the cost of  
17 the study. We do need to develop objective endpoints  
18 or definitions of endpoints that take the guess work  
19 out of the final assessment for the investigator and  
20 take out that bias. But that is certainly possible.  
21 We can use when cases of wound healing studies or  
22 ulcer studies, we can use tracings for computer  
23 analysis. We can use photographs. Certainly start  
24 out with some very definitive definitions of complete  
25 healing such as epithelial layer, presence of

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 epithelial layer, lack of drainage, and then we can  
2 also add patient follow up to confirm the next week,  
3 for instance, that total healing has in fact taken  
4 place.

5           When you're dealing with issues of  
6 complete wound healing in chronic ulcers, frequently  
7 the discussion of the need for wound biopsies or the  
8 value of wound biopsies come up. And this is not  
9 always, again, a practical measure of complete healing  
10 or even an assessment, or an opportunity for an  
11 assessment, of the type of healing that has taken  
12 place. In many cases, once these very chronic long  
13 term ulcers have healed, patients are not going to  
14 want to, and physicians are not going to want to ,  
15 rebiopsy that wound, inflicting additional trauma to  
16 that wound when we finally had success in this case.  
17 We certainly have seen in the literature where these  
18 types of insults cause recurrence of the ulcers and in  
19 many cases the IRBs and physicians consider this to be  
20 unethical. So, we need to consider the value of these  
21 kinds of measures.

22           So, in conclusion, certainly chronic wound  
23 healing studies can be well controlled but the  
24 definition of that good control really must remain  
25 flexible enough. We need to -- it's very important to

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 separate out what is essential information from non-  
2 essential information, in light of the fact that we're  
3 dealing with a very specific patient population wh o  
4 have had these wounds for a very long period of time  
5 and to have actually very active lives to conduc t  
6 under the circumstances.

7 Thank you very much.

8 CHAIRMAN McGUIRE: Thank you.

9 We have a representative this morning fro m  
10 the Wound Ostomy Continence Nurses Society, Ms. Ruth  
11 Bryant.

12 MS. BRYANT: Good morning. My name i s  
13 Ruth Bryant. I am a clinical nurse specialist i n  
14 wound care. I've been a clinical specialist for the  
15 past 15 years. I'm also the past president of th e  
16 Wound Ostomy and Continence Nurses Society which is an  
17 organization of 4,200 members dedicated to the care of  
18 patients with wounds, ostomies, and incontinence. An d  
19 in 1998, we'll be celebrating our 30th anniversary, s o  
20 we've been around of ra while.

21 The committee members already have a copy  
22 of our response to questions for consideratio n  
23 concerning clinical trial designs for chroni c  
24 cutaneous ulcers. And on behalf of the WOCN, what I' d  
25 like to do is just take a few minutes to add som e

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 comments addressing clinical care specifically that  
2 would ultimately relate to clinical trial design and  
3 to adoption of clinical trial results and to clinical  
4 practice.

5 I represent an organization of nurses who  
6 have championed chronic wound care before it was in  
7 vogue, when the only wound care product available was  
8 gauze, before moist wound healing itself was even  
9 widely accepted or considered standard care. Nurses  
10 have played a key role in the introduction and  
11 acceptance of transparent dressings, hydrogels,  
12 hydrocolloids, and the many other wound care products  
13 that we enjoy today. So, we are thrilled with the  
14 advent of interactive products that combine modalities  
15 that are demonstrated to be efficacious and we are  
16 concerned about how clinical trial designs will occur  
17 in wound care.

18 We've also played a key role in educating  
19 nurses and physicians in comprehensive wound  
20 management, stressing the need to manage the disease  
21 process while optimizing the topical wound  
22 environment. The clinical reality is that nurses  
23 provide much of the wound care in the United States.  
24 Our involvement can range from identification of ulcer  
25 etiology, wound assessment, treatment selection, and

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 conservative sharp debridement to simply application  
2 of prescribed treatment. The generalist health care  
3 provider, be that a nurse or a physician, will b e  
4 prescribing and applying products and there is a  
5 strong potential for misdiagno sis of ulcer types, for  
6 over utilization of products, and this has alread y  
7 been demonstrated through some of the things that have  
8 happened with HCFA and claims that have been made for  
9 products, because we all know more is better fo r  
10 wounds, or we think they are. And inadequat e  
11 attention to critical comprehensive patient car e  
12 issues such as offloading, management of share d  
13 forces, and adequate glucose control.

14 In many health care settings it will b e  
15 the nurse who discovers the foot ulcers, who rolls th e  
16 patient over and finds the pressure ulcer, and the n  
17 who relays that information to the physicians an d  
18 obtains the order for topical care, often times ,  
19 actually, requesting a specifi c product or a specific  
20 intervention. Wound care nurses have long advocated  
21 for extensive debridement of neuropathic ulcers ,  
22 adequate debridement of pressure ulcers, an d  
23 encouraged appropriate management of venous ulcers .  
24 However, every day we encounter reluctance to debride .  
25 We encounter reluctance to moist wound healin g

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 techniques. And we encounter impediments to  
2 appropriate comprehensive care.

3 As new products become available, as new  
4 clinical trials unfold, extensive education programs  
5 as essential and it should include nurses. And it  
6 should address comprehensive wound management in  
7 addition to adequate debridement. Ideally, the WOCN  
8 would love to see the incorporation of phrases such as  
9 "this product is intended for use in conjunction with  
10 a comprehensive management approach under the  
11 direction of a physician or a wound care specialist."

12 We support the extensive investigation of  
13 safety of new products. We think there's a lot of  
14 room for improvement in that area. And we appreciate  
15 the specific direction on the appropriate size of  
16 ulcer application for these products because all too  
17 often these wounds are huge and there's a lot of  
18 opportunity for absorption. We also appreciate the  
19 labeling of products to be specific so that the  
20 products actually address whether they're indicated  
21 for a Stage 2, Stage 3, or the extent of the ulcer  
22 that they're appropriate for, so that they will  
23 curtail inappropriate use of products on extremely  
24 shallow wounds.

25 Must has been said about education in the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 past. The assumption is that education will approve  
2 aggressive debridement, compliance, offloading, e t  
3 cetera. The fact that there are many other factor s  
4 that influence compliance such as access to offloadin g  
5 devices, diabetes monitoring equipment, lymphedem a  
6 control. Much research is needed looking into these  
7 other issues because the topical management o r  
8 whatever we identify will not be sufficient in and of  
9 itself. Topical care cannot be seen as a panacea ,  
10 otherwise we will see anyone who breaks down with an  
11 ulcer again recur with the ulcer because they have no t  
12 treated the underlying pathology.

13 Topical care is a short term f ix. All of  
14 us would love to see the long term pay offs. We love  
15 to see the wound heal. But we cannot lose sight of a  
16 need to assure access to products and resources s o  
17 that patients can actually manage their underlyin g  
18 disease. We applaud the activ ities by FDA to look at  
19 chronic wound management and appropriate clinica l  
20 trial design. We also applaud actions by HCFA whic h  
21 include providing diabetes management supplies an d  
22 studying the efficacy of support services an d  
23 lymphedema devices because we believe these activitie s  
24 actually dovetail very nicely with the current topic  
25 of wound care.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 In closing, as wound care specialists, th e  
2 WOCN is eager to support advancement of clinica l  
3 practice based on scientific evidence and we are eager  
4 to work with participants here in future endeavor s  
5 involving the care of patients with chronic or acute  
6 wounds.

7 Thank you.

8 CHAIRMAN MCGUIRE: Thank you, Ms. Bryant.  
9 That was a very thoughtful statement.

10 I think now we work. Would, Doctor Weiss ,  
11 would you like to make an introductory statement?

12 I think many of you have the document we  
13 will be working from. If not, these have bee n  
14 distributed to industry. There are also copies in the  
15 foyer. And we will be following the document fairly- -  
16 Well, I don't know. We intend to follow it fairl y  
17 carefully.

18 DOCTOR WEISS: Good morning. If I can ge t  
19 the first slide. I just have a few overheads just to  
20 give the committee and the aud ience a little bit of a  
21 background on how we got to where we are today.

22 First of all, as hopefully many people ar e  
23 aware but maybe not everybody, there are, of course,  
24 three centers within the Food and Drug Administration  
25 that are involved in reviewing products for medica l

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 use. And all three of these centers have th e  
2 jurisdiction to review products that are being use d  
3 for wound healing, the Center for Biologics, th e  
4 Center for Devices, and the Ce nter for Drugs. And on  
5 the overhead are just examples of some of th e  
6 different types of products that are under the purvie w  
7 of each of the different centers.

8 (SLIDE CHANGE)

9 Now, in addition to this division, there  
10 is also a inter-center wound healing clinical focu s  
11 group. And this focus group is, I think, somewha t  
12 unique within the agency because it has members that  
13 are reviewers from all three centers that are involve d  
14 in the review of products for wound healing. Th e  
15 mission of this focus group is to expedite developmen t  
16 of products for wound healing. The functions of this  
17 group are to enhance consistency of the reviews acros s  
18 the centers, to share information from all parts o f  
19 the agency, to provide a forum for clinical proble m  
20 solving, and to act as a direct tri-center liaiso n  
21 from the FDA to academia and to industry and othe r  
22 types of organizations.

23 Now, there have been opportunities alread y  
24 where members of the focus group have been able t o  
25 comment and serve as a representative of the agency t o

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 various organizations. Back in March of 1993, the FDA  
2 sponsored a wound healing workshop. This was held at  
3 Masur Auditorium on the NIH campus. Subsequently,  
4 members of this group published an article, Regulatory  
5 Concerns for Wound Healing Biologics, and a copy of  
6 that article is in your information packets.

7 The members of the tri-center clinical  
8 focus group have also had the opportunity to interact  
9 with various types of organizations. The government  
10 relations committee of the Wound Healing Society,  
11 there's a specific response that the members of the  
12 wound healing group published in response to a number  
13 of comments and questions from the Wound Healing  
14 Society. Members of the group also met with this  
15 particular committee of the wound healing society and  
16 there was a very good interactive discussion. There  
17 was also a period of time where the group was able to  
18 interact with the federal issues committee of the  
19 American Burn Association. And then representatives  
20 also met with members of the European Tissue Repair  
21 Society for discussions on wound pharmacology.

22 Now, as part of this process to develop a  
23 policy on wound healing, the FDA is seeking input from  
24 this advisory committee, other advisory committees,  
25 from our pharmaceutical manufacturers, from various

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 professional organizations, and other intereste d  
2 parties. The Wound Healing Clinical focus group i s  
3 taking the lead in developing what's known as a  
4 guidance document.

5 (SLIDE CHANGE)

6 As part of this process, then, we are her e  
7 today to have the beginning of this discussion .  
8 Today's discussion will be a s cientific discussion of  
9 cutaneous ulcers and this is a discussion that's goin g  
10 to involve a number of different areas, as you can se e  
11 from the agenda. The purpose of this is to reall y  
12 start to get some ideas about what should be in th e  
13 document, what should the scope of the document be .  
14 This will be followed by further scientifi c  
15 discussions, hopefully in the fall, at this sam e  
16 advisory committee, hopefully with als o  
17 representatives from the general practice committee,  
18 to discuss acute burn healing. And we hope with all  
19 the comments that we get back, to be able to issue a  
20 first draft of the guidance document.

21 Now, as part of our procedures for goo d  
22 guidance, this is a policy that was just put out i n  
23 February of this year. There's a new procedure ou t  
24 now for how we should seek inp ut and develop guidance  
25 documents from the agency. As part of that process,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 we are seeking early input such as we are today. Even  
2 before we issue the first draft of the guidance  
3 document, we are putting out a available for the public  
4 and for other interested parties the opportunity to  
5 comment, like I said, even before we have the first  
6 draft of the document available.

7 This particular discussion point, the  
8 document that we're going to discuss today, is  
9 available on the Web. We've already received comments  
10 from a number of interested parties. We hope to get  
11 more comments back from the outside as well as from  
12 members of the committee, from people at this  
13 discussion today. We're going to take all of those  
14 comments and with that, we hope, like I said, to issue  
15 a first draft of this document. The draft, then, will  
16 be put out in the Federal Register and out on  
17 electronic system for comment prior to having a  
18 further discussion at an advisory committee.

19 Now, we hope -- we have a little bit of an  
20 ambitious agenda but we hope in the spring, perhaps,  
21 of next year, to be able to have a further discussion  
22 at this meeting about the guidance document.

23 And finally, I would like to acknowledge  
24 in particular the members of the Wound Healing Clinic  
25 focus group that have taken the lead in getting to

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 where we are today. And those are people wh o  
2 represent all the three centers that I've mentioned.  
3 There's Doctor Durfor and Gail Gantt from the Center  
4 for Devices; Betty Goldman who especially has bee n  
5 very helpful in getting this d ocument and making sure  
6 that we're keeping in line with the guidanc e  
7 practices; Doctor Lou Marzella; Kathy O'Connell from  
8 Center for Drugs; and then Mer cedes Serabian and Kurt  
9 Stromberg, and Doctor Tiwari a lso from the Center for  
10 Biologics.

11 Thank you very much.

12 CHAIRMAN McGUIRE: Thank you, Docto r  
13 Weiss.

14 Well, that's our charge. The clinica l  
15 focus group would like to be able to design a guidanc e  
16 document and they have posed six topics for us t o  
17 discuss over the course of the day. And I think we'l l  
18 begin by reading the -- Again, if any of you want thi s  
19 document, there's some outside.

20 The first topic is standard of care. I  
21 won't enumerate the other five. We'll go through the m  
22 sequentially.

23 The state -- I'll read the statement firs t  
24 and then the question. And then what I'll do is ask  
25 for participation from the advisory committee.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1                   Variability of wound management in a trial  
2                   may lead to variability of outcome and decreased power  
3                   of the trial to detect differences in outcome. Use of  
4                   protocol defined standardized care would address this  
5                   concern but might preclude difference center's  
6                   preferences or individualized therapy for a specific  
7                   patient's need and may not reflect the way a product  
8                   will be used by practitioners.

9                   The question is, how important is it to  
10                  designate the type or range of types of standard care  
11                  that should be used in a multi-center clinical trial  
12                  for each of the three major ulcer types?

13                  Who would like to start this morning?

14                  DOCTOR BERGFELD: I'd like to start this.  
15                  Having listened very intently yesterday at all of the  
16                  different experts who actually deal with these wounds  
17                  and being a dermatopathologist and a clinical  
18                  dermatologist, the thing that I heard that was common  
19                  to everyone, that the standards of care are only known  
20                  by those experts who deal with ulcers continuously in  
21                  their practices. And it seems relevant to me that  
22                  standards of care need to be developed by some group  
23                  as to what is the basic standard of care and the  
24                  techniques of care. I think that could be a very  
25                  important issue here today.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 I think that this information then needs  
2 to be disseminated in a number of routes, not only by  
3 the guidance document that's being developed but into  
4 the various specialties as -- and be approved by these  
5 various specialties incorporated into their education  
6 of their teaching facilities for their residents and  
7 their physicians. Because, I believe that this is a  
8 major area that is not delved into or not even  
9 standardized in the teaching settings, of how to care  
10 for these wounds. I think it's been overlooked and I  
11 think that this information would serve great purposes  
12 in caring for these chronic ulcer patients. I heard  
13 this.

14 And the other thing is to declare  
15 something that was stated yesterday on infection  
16 control which deals with standards of care as well,  
17 and define that well.

18 CHAIRMAN MCGUIRE: Thank you, Doctor  
19 Bergfeld.

20 Would someone like to add to that or --

21 DOCTOR COOPER: Diane Cooper.

22 CHAIRMAN MCGUIRE: Yes.

23 DOCTOR COOPER: I would like to state that  
24 I thoroughly support what you said and I think that if  
25 we're going to do clinical trials and we don't have

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 standards, and we have so much variability, we ge t  
2 ourselves into more trouble be cause we've spent a lot  
3 of money and time to assess something and then w e  
4 can't make really a strong statement about it either  
5 way.

6 But I would like to suggest that thos e  
7 standards of care, many of them have been evolved ove r  
8 time with clinical trials that have been done by thes e  
9 leading authorities and that perhaps one of th e  
10 methods of accelerating the achievement of havin g  
11 those be spread wider would be to review studies o f  
12 clinical wound times, namely the diabetic ulcer ,  
13 chronic venous ulcer, and the pressure ulcer, an d  
14 extract many of those which I think are becoming more  
15 and more consistent if you look at the literature.

16 I think, also, though that there ar e  
17 certain wounds that present a real difficulty wit h  
18 standardization because of cost. I think the diabeti c  
19 and the venous ulcer are primarily outpatien t  
20 ambulatory wounds. But the pr ессure ulcer frequently  
21 in order to study the person w ith the pressure ulcer,  
22 they have to be hospitalized f or some time. And that  
23 makes it very difficult, parti cularly if they have to  
24 have the ulcer saucerized before or they undermining  
25 debrided before they're entered into a study, the y

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 have to be in the hospital.

2 And I currently work at the VA hospita l  
3 where we are allowed to keep our patients in th e  
4 hospital but I have previously in my life worked i n  
5 private hospitals where I know that would b e  
6 impossible. And I also know other investigators who  
7 work with us in multi-center trials who cannot kee p  
8 those kinds of patients in hospital. So, dependin g  
9 upon distance, support service s at home, et cetera, I  
10 think the pressure ulcer is becoming increasingl y  
11 difficult chronic wound to study with extrem e  
12 standardization.

13 CHAIRMAN MCGUIRE: Thank you. I'd like t o  
14 put in a footnote here. Implicit, I think, in the wa y  
15 the discussion is developing i s that we all recognize  
16 different standards of care fo r the three major ulcer  
17 groups . And if there's any disagreement with that ,  
18 let's get that out.

19 The other topic that I think we're no t  
20 really going to be addressing very directly but that  
21 is prevention. And in different centers there ar e  
22 different teams that look for different signs fo r  
23 pressure ulcers, for diabetic ulcers, and I propos e  
24 that that be a piece of this g uidance even though the  
25 guidance is directed toward developing clinical trial s

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 after the ulcer has been formed.

2 The point that came up yesterday over an d  
3 over again, although I think it was addressed fairly  
4 directly, is that protocol defines standards of care  
5 are in general superior to standards of care. I n  
6 other words, the better definition there is in th e  
7 protocol for standard of care, the more -- the care i s  
8 superior.

9 Yes, Doctor Lipsky.

10 DOCTOR LIPSKY: When we use the ter m  
11 standards of care, my understanding is that this is an  
12 appropriation of an essentially legal concept. When  
13 one testifies in a legal syste m, the attorneys act as  
14 if when you graduate from a professional school ,  
15 you're issued a book that's la beled standards of care  
16 and you look up what you're supposed to do. And i f  
17 you fail to meet those standards, you are then hel d  
18 liable in the legal system.

19 So, I think we ought to be careful about  
20 what we mean by that and the standards of care fo r  
21 conduct of a study may be different from the standard s  
22 of care to which a busy practitioner might be hel d  
23 accountable. I think that the committee ought to see k  
24 legal guidance in addition to guidance from healt h  
25 professionals when we use those terms.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           The other issue I think we need to address  
2           is which professionals ought to be able to do the  
3           various kinds of care that we're talking about. Right  
4           now I don't know whether it's defined who can do wound  
5           debridement, for example. In my antibiotic research  
6           and diabetic foot clinics, I have a nurse who has been  
7           trained to do that and does it very well. But I  
8           actually don't know what the legal guidelines are for  
9           that and whether they vary from state to state. And  
10          I think a statement from these organizations would be  
11          helpful in allowing people who are trained regardless  
12          of what their professional license may be to do the  
13          work rather than allowing people to do the work who  
14          have a particular license but haven't been trained.

15                   CHAIRMAN MCGUIRE: Doctor -- Lynn wanted  
16                   to make a comment.

17                   Doctor Drake.

18                   DOCTOR DRAKE: You know, I've been  
19                   involved in the guideline and standard developments  
20                   for many years and what I can tell you is that it's  
21                   extraordinarily difficult. And the second you set a  
22                   standard, somebody's going to come along right behind  
23                   you and modify it. I really want to echo what Doctor  
24                   Lipsky said, that legally you can get in all kinds of  
25                   quagmire with this.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 I think -- I don't like the word standard  
2 because it implies a defined way to do something that  
3 must be done over and over. I think guidelines or  
4 some other terminology is better. Writing --  
5 Developing standards of care is extraordinarily  
6 difficult because, first of all, there's precious  
7 little data in any area on which to -- upon which to  
8 base your decisions, if you want to build in ironclad  
9 decisions.

10 If you want to do a meta analysis, the  
11 literature is extraordinarily expensive to do so and  
12 time consuming, and manpower intensive. And so, I  
13 think we have to be very careful. I think there's --  
14 I agree, I think there's one role, perhaps designing  
15 guidelines for conduct of a clinical research study in  
16 this arena. But to define the standards of care for  
17 wounds I think is an impossible task and just fraught  
18 with difficulties. And almost designed for failure at  
19 the onset unless we back up and take a more  
20 incremental approach to the issue.

21 DOCTOR WITTEN: I just would like to make  
22 a little comment here as far as what we are asking you  
23 about. And I think maybe it would be more appropriate  
24 to call it standardization of care for the purposes of  
25 a trial rather than what is the standard of care for

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 that type of ulcer.

2 CHAIRMAN MCGUIRE: Yes.

3 DOCTOR WITTEN: Because there may be more  
4 than one way to address a given type of ulcer and I  
5 think we're more interested in some guidance from you  
6 all on how to standardize for a particular trial, how  
7 to characterize what the therapy would be.

8 CHAIRMAN MCGUIRE: That's an important  
9 distinction.

10 Doctor Bergfeld, you had a question?

11 DOCTOR BERGFELD: Yes, I was just going to  
12 come back to the term standards of care. If you heard  
13 me correctly when I first made my statement, I said  
14 basic care. And I think that also is different. But  
15 I would state that if the FDA needs a care package of  
16 how to handle these wounds, whatever you call them,  
17 that that should in some way have some commonality for  
18 all the studies.

19 CHAIRMAN MCGUIRE: Doctor Thomas is up.

20 DOCTOR THOMAS: I wanted to echo what  
21 you're saying because I think that's the issue of the  
22 question. What I see in the design of clinical trials  
23 is that often the control arm is an arm that would not  
24 be used in clinical practice. And so, comparison of  
25 the two to that particular treatment arm and we saw

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 some of that yesterday when we were talking.

2 What we need to look at is that if we know  
3 that there is a generally accepted pattern, and we  
4 don't always know that for everything, but for  
5 example, compression for venous ulcers. Then if  
6 that's considered to be an important part of clinical  
7 care that's followed most of the time, then the  
8 control arm and the treatment arm should include that.

9 And particularly in the work that I do in  
10 pressure ulcers, often we're comparing the treatment  
11 arm to treatments that are no longer in vogue or no  
12 longer in use, or, for example, moist healing. I  
13 think all of us would do that. So, the control arm in  
14 that situation should be that.

15 So, my response to this was that the  
16 agency should look at control arms and try to define  
17 in some sort of way a reasonable expectation that that  
18 is a commonly used and generally accepted practice  
19 rather than some control arm that has no meaning.

20 CHAIRMAN MCGUIRE: Doctor Mustoe.

21 DOCTOR MUSTOE: I think one of the  
22 problems, and I think I would follow along with what  
23 Doctor Thomas said, that I think the key issue here is  
24 that there are only a few very basic principles which  
25 everybody accepts as standard such as compression for

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 venous stasis, offloading for diabetic ulcers, moist  
2 healing. Debridement, interestingly, is the issue  
3 that perhaps, or keeping the wound clean, is perhaps  
4 the single biggest issue that can impact a wound, and  
5 yet it's extremely difficult to define what good  
6 debridement is in a standardized way.

7 So, I think that the key issue should be  
8 that you accept three or four standards, such as  
9 pressure relief, moist healing, cleanliness, and then  
10 develop ways to define whether or not you're achieving  
11 it. For instance, if someone can daily wrap a venous  
12 stasis ulcer in the same skillful way that a once a  
13 weekly dressing is made, then the two of them should  
14 be considered equivalent. The key issue is can you,  
15 and I think in that case, by leg circumference, you  
16 can measure it. But I think you really are going to  
17 have to have a menu of standards and the wound, as we  
18 heard yesterday, chronic wounds are so variable that  
19 there is not certainly any studies right now that are  
20 going to prove that one "standard" is better than  
21 another. And I think the key area has got to be  
22 defining that you've achieved the same goal in both  
23 arms of the trial and not a rigid adherence to one  
24 standard.

25 CHAIRMAN MCGUIRE: So, Tom, you're saying

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 there should be three menus fo r the three major types  
2 of defect. And then there would be some variability  
3 in those menus and an attempt should be made to find  
4 equivalents within those menus?

5 DOCTOR MUSTOE: Absolutely. For instance ,  
6 in diabetic ulcers you might have two or three method s  
7 of offloading. But if you can measure the amount of  
8 callus generated carefully, it may be that tw o  
9 entirely different offloading devices are equivalent.  
10 And because one patient is going to be able to use an d  
11 another is going to have to use another, if you set u p  
12 your trial so that you all have to use the sam e  
13 offloading device, you make th e trial very difficult.

14 I think the issue is can you define i f  
15 both were offloaded to an appr opriate degree. And if  
16 you can, I think that should be -- both should b e  
17 acceptable. It's just a measure of being able t o  
18 define them.

19 CHAIRMAN MCGUIRE: Doctor Mindel.

20 DOCTOR MINDEL: Whenever you use othe r  
21 treatments, you confound the interpretation of you r  
22 attempted treatment. And in ulcers, you're no t  
23 dealing with a life threatening situation. I'd like  
24 to make the argument that no t reatment be used when a  
25 treatment is being tested, but that you have a n

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 assessment of worsening that is a reasonable  
2 assessment of worsening. And the trial, the person in  
3 the trial, could be removed from that trial as soon as  
4 there was an indication that the condition had  
5 worsened.

6 CHAIRMAN MCGUIRE: That should get some  
7 discussion.

8 DOCTOR THOMAS: No treatment, is that what  
9 he said?

10 DOCTOR MINDEL: No treatment other than  
11 the treatment under consideration. For example,  
12 debridement might interfere with the effect of a drug,  
13 or moisture might impair the frequency of --

14 DOCTOR THOMAS: I don't think there's any  
15 way, number one, I personally could do that. Or  
16 number two, that my IRB would let me do that.

17 CHAIRMAN MCGUIRE: Doctor Rosenberg had a  
18 remark.

19 DOCTOR ROSENBERG: First of all, I just  
20 would like to commend the agency for its efforts in  
21 this inter-group serious discussion of a major problem  
22 that really does touch on many bases. It has to be  
23 handled in this way.

24 One of the presentations we heard this  
25 morning mentioned the usefulness of historical

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 controls. Of course, those are not adequate fo r  
2 deciding on the effectiveness and safety of an agent  
3 without proper placebo controls. But, the idea o f  
4 historical controls, what are the outcome s  
5 historically expected for this condition, really ough t  
6 to be built into these things. And it's so hard t o  
7 find them. They're not in most of the publishe d  
8 guidelines. They're not in many textbook articles .  
9 And yet, it underlies everything. And unless yo u  
10 appreciate that, you really can't know these things.

11 But a group such as you are organizing ca n  
12 with experienced people who actually work in thes e  
13 fields come up with some realistic ranges that pu t  
14 everything into perspective and ought to be there .  
15 And for instance, we heard yesterday that the outcome s  
16 from patients treated with offloading heal diabeti c  
17 ulcers much more quickly than those treated with a n  
18 agent that we studied.

19 And I think those are the kind s of things  
20 that HCFA wants to know. And while the FDA' s  
21 legislative mandate is not the same as HCFA's, I thin k  
22 all of us are obliged to read the newspapers and t o  
23 think in general terms of outcomes also.

24 CHAIRMAN MCGUIRE: Doctor Miller, to m y  
25 left.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DOCTOR CLINTON MILLER: Thank you. I'd  
2 like to return to the question.

3 It says, how important in a multi-center  
4 trial. And the question acknowledges the existences  
5 of the three major ulcer types. It's mandatory .  
6 That's all there is to it. You have to have in a  
7 multi-clinic trial and talk about practice. If you're  
8 going to make comparisons, then the conduct of tha t  
9 design has to be the same in each of those centers .  
10 It's mandatory. They need to put these things out.

11 The other thing is that we tal ked a while  
12 ago, or yesterday, about the complexity of this an d  
13 the dynamics of these various kinds of ulcers. Th e  
14 more complex they are, the more difficult it is t o  
15 find an article in the literature that can duplicate  
16 these same circumstances of care that you ar e  
17 proposing. Therefore, the value of historica l  
18 controls goes down as the complexity goes up.

19 So, I think that, yes, it's a good ide a  
20 for us to accept those histori cal controls where they  
21 can be found. But I don't thi nk you're going to find  
22 very many of them. So, you better be prepared an d  
23 encourage the development of appropriate contro l  
24 groups for that particular single design you'r e  
25 proposing for these multiple sites.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Thank you.

2 CHAIRMAN MCGUIRE: Yes, Doctor Miller.

3 DOCTOR FRED MILLER: I think as we discuss  
4 standards --

5 CHAIRMAN MCGUIRE: This is Doctor Miller  
6 to my right for the --

7 DOCTOR FRED MILLER: Fred Miller to the  
8 right.

9 As we discuss standards of care, or basic  
10 principles in therapy, I think that we have to look at  
11 the pathogenesis and what we know the pathogenesis  
12 and of the etiologic factors. For example, with the  
13 neuropathic diabetic ulcers, we know that these are  
14 caused by friction and pressure on abnormal bony  
15 prominences in a person with an insensate foot. So  
16 that in any trial, offloading is absolutely a sine qua  
17 non if you're going to heal the lesion. We also know  
18 in those lesions that debridement is essential.

19 In the venous ulcers, we know that venous  
20 hypertension plays a critical role. So that in any  
21 trial, the venous hypertension has to be controlled  
22 before you can begin to evaluate agents.

23 So, I think these are very basic  
24 principles that must be adhered to when you're doing  
25 a trial. You have to look at the basic pathogenesis

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 and the etiologic factors, and then begin to use your  
2 various agents. But you have to control these factors  
3 first.

4 CHAIRMAN McGUIRE: Fred, let me ask you a  
5 question. Do you think if I gave you the three major  
6 wound categories that you could generate expectations  
7 for care that would be generally agreeable?

8 DOCTOR FRED MILLER: You know, I guess I  
9 would look first at the diabetic ulcer and I think I  
10 probably could. Yes.

11 CHAIRMAN McGUIRE: But you would be able  
12 to identify characteristics of care for occlusive  
13 ulcers that would certainly be different than the  
14 diabetic neuropathic ulcers?

15 DOCTOR FRED MILLER: I think ulcers are  
16 going to vary, types of ulcers. But again, if I would  
17 begin with the basic pathogenesis of what we know of  
18 the pathogenesis, I would think yes, we could come up  
19 with some basic standards and then from there get  
20 there.

21 CHAIRMAN McGUIRE: Well, I mean at the  
22 very simplest, the compressive therapy that we use for  
23 venous stasis ulcers is just perhaps one of the worst  
24 mistakes you can make with an occlusive ulcer because  
25 you further compromise the arterial insufficiency.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DOCTOR FRED MILLER: I guess I'd want to  
2 know how you're defining occlusive ulcer.

3 CHAIRMAN MCGUIRE: I'm sorry, I'm talking  
4 about an arterial.

5 DOCTOR FRED MILLER: You mean an arterial ?

6 CHAIRMAN MCGUIRE: Yes.

7 DOCTOR FRED MILLER: Yes, certainly.

8 CHAIRMAN MCGUIRE: Yes.

9 Ms. Cohen.

10 MS. COHEN: I'm very interested in what  
11 you all have to say and I'm trying to think as a  
12 consumer who might not know anything, probably  
13 doesn't, about what is happening to them. I need to  
14 know how important the patient, what role the patient  
15 plays, in the cure. I mean, it's been very clinical,  
16 the discussion, but can you separate some things that  
17 you know in common denominators for patients that will  
18 help effect a better cure? And I think information is  
19 part of it. Because if you're going to be part of the  
20 process when you're trying to have a cure, then you  
21 also have to understand the patient mind and what they  
22 need to do in order to effect a more realistic cure.

23 And I don't know whether that's historical  
24 or what it is but I'm trying to understand the  
25 consumer in all of this. You can set all the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 standards you want but if they don't do what they're  
2 supposed to do, I don't know how effect the cure is.

3 CHAIRMAN MCGUIRE: You're bring ing up the  
4 issue of compliance and which has been mentione d  
5 several times yesterday and several times today.

6 MS. COHEN: How can you separate it ,  
7 though? If you want to set up some clinical rules ,  
8 how can you separate that?

9 CHAIRMAN MCGUIRE: You accept compliance  
10 or lack of compliance as one o f the variables and you  
11 do your best, I think, to establish some homogeneity  
12 in the trial group. But compliance, the fact tha t  
13 we're not talking about compli ance, doesn't mean that  
14 we don't consider it to be a k ey feature. I think we  
15 would all like for that issue to go away because it's  
16 so difficult to control. But it is a major issue.

17 The other issue is -- I mean, compliance  
18 is really very complex because it depends not onl y  
19 upon the patient's interest in complying, or working  
20 with the health care provider. It depends upo n  
21 comprehension and it also depe nds upon who else is in  
22 the household, who else can provide back up. I t  
23 depends upon rather fundamental things lik e  
24 transportation, how do you get there. This is -- it' s  
25 a very important and very complex issue.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 MS. COHEN: I -- Wilma wants to say  
2 something now.

3 CHAIRMAN MCGUIRE: Susan, go ahead and  
4 make --

5 MS. COHEN: Yes. I'm just concerned about  
6 this whole process and under clinical trials it's the  
7 most optimum atmosphere you could find. But if you  
8 have that, but you don't understand what the patient  
9 is really going to do, then clinical trials are going  
10 to be far more successful than the actually of someone  
11 who comes into your clinic to have a wound treated.

12 CHAIRMAN MCGUIRE: Susan, what I'm saying  
13 is that I think --

14 MS. COHEN: I heard you.

15 CHAIRMAN MCGUIRE: I think most people are  
16 aware of the problem. It's a major problem.

17 Doctor Miller, you're up.

18 DOCTOR CLINTON MILLER: I would like to  
19 support her position. It seems to me that what we're  
20 asking is there -- and what we've talked about in the  
21 past is a standard of care from an acute point of  
22 view. I think that when you're going to start talking  
23 about the development of that standard of care, it  
24 needs to be extended into the other environments that  
25 the patient lives in. And it needs to be spelled out .

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 It needs to be explicit with regards to patient  
2 education, the care giver education, and all of the  
3 other activities that are associated with the overall  
4 care program. And that's something that our standards  
5 of care do not normally specify.

6 CHAIRMAN MCGUIRE: Doctor Mustoe.

7 DOCTOR MUSTOE: I guess I would also tend  
8 to agree that chronic wounds differ from most other  
9 disease processes in the sense that a patient who's  
10 truly compliant may be spending an hour or two a day  
11 cleaning and dressing their wound and may also be  
12 significantly modifying their lifestyle. And most  
13 diseases really compliance requires taking a couple of  
14 pills so that the variability in compliance is, I  
15 think, extraordinary in chronic wounds. And I don't  
16 think if you specifically acknowledge that, in fact I  
17 would say that's the single biggest issue in of  
18 fitting chronicity.

19 So, I guess to me, where standards come up  
20 is that if -- it's true you can't get rid of  
21 compliance. But if you don't really force, in setting  
22 up a trial, very explicit measures of compliance, I  
23 think you missed the boat. And I think that that's  
24 certainly something I saw yesterday is probably not --  
25 if the only answer is the investigator on a weekly

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 visit saying is the patient complying or not, that's  
2 a very subjective. And I guess I'd like to see some  
3 increased attention to determining what compliance is .  
4 Not so much did they apply the treatment, i.e., th e  
5 medication, but how long did they spend cleaning their  
6 wound, other issues such as that. So, I do think it  
7 is a key issue in chronic wounds.

8 CHAIRMAN MCGUIRE: Given we cannot carry  
9 out trials routinely in a general clinical researc h  
10 center, it's going to be gener ally a less controlled,  
11 less rigorous environment than that, then that put s  
12 all the more pressure on us to identify the variables  
13 in the home. And the point th at Ms. Cohen brought up  
14 are difficult but real points.

15 DOCTOR ROSENBERG: Could I spe ak to that,  
16 Doctor McGuire, what you just said?

17 CHAIRMAN MCGUIRE: Yes, Doctor Rosenberg.

18 DOCTOR ROSENBERG: I was just thinking ,  
19 just in those lines. I mean, we're familiar with the  
20 clinical research centers whic h have been funded over  
21 the years by the National Institute Health fo r  
22 purposes of doing metabolic studies primarily tha t  
23 have to be done in the hospital.

24 Considering the millions of -- th e  
25 billions of dollars that are spent on wound care and

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1       how -- and other, perhaps, comparable clinica l  
2       problems, I think it would not be inappropriate fo r  
3       HCFA and the FDA together to seek a legislativ e  
4       mandate for some few carefully chosen five-bed units  
5       in places like Wayne State and Johns Hopkins, an d  
6       Stanford, and Cleveland clinic, to do studies lik e  
7       that. I think the cost in ter ms of all this going on  
8       would be quite reasonable.

9                   CHAIRMAN MCGUIRE: You meant they would b e  
10       quite reasonable to you?

11                   DOCTOR SIMMONS-O'BRIEN: No, in the end.

12                   CHAIRMAN MCGUIRE: In the end.

13                   Doctor Lavin.

14                   DOCTOR LAVIN: Yes, a point I'd like t o  
15       make is obviously from all the discussion we've heard  
16       here so far, it's very complex choosing a standard of  
17       care or standardized care. And I think that thi s  
18       really can be best addressed by having pilot studies  
19       before one goes into major pha se 3 investigations. I  
20       think that a pilot study can work out a lot of these  
21       bugs, a lot of these logistics, and a lot of thes e  
22       differences that are likely to come up betwee n  
23       centers. And while it's admirable to have a n  
24       inpatient setting to do some of these studies, i t  
25       really won't be realistically feasible for all o f

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 these other studies that are going to have to be done  
2 on an outpatient basis.

3 CHAIRMAN MCGUIRE: Doctor Marzella, what  
4 points have we not touched on this area? Caught you,  
5 didn't I. I didn't mean to.

6 DOCTOR MARZELLA: I think that we've heard  
7 a very good discussion. I wanted a clarification  
8 about the issue of compliance. I understand from the  
9 committee that that should be part of the document?

10 CHAIRMAN MCGUIRE: Well, I think  
11 compliance is such a big part of it that we tend not  
12 to discuss it, because it's just -- it's so complex.  
13 And Doctor Mustoe said that it's compliance with  
14 chronic ulcers is much different than taking a couple  
15 of pills a day. Well, my patient population has  
16 trouble taking a couple of pills a day. And so,  
17 compliance starts at a very low level.

18 DOCTOR MARZELLA: We would also welcome  
19 additional -- we would welcome additional input from  
20 the committee. We've heard some individuals  
21 volunteering to provide additional information and we  
22 would welcome receiving that.

23 DOCTOR COOPER: I think that compliance is  
24 also very important but I think that one method of  
25 getting more compliance is again what we heard

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 yesterday, that we need more homogeneity among  
2 investigators. And all I do is clinical trials and  
3 all I do primarily is outpatient clinical trials. I  
4 mean, increasingly, as I said, inpatient trials are  
5 decreasing.

6 And one way we effect compliance is that  
7 we thoroughly go over the -- explaining the study to  
8 the individual and really stress do you understand .  
9 Do you have any questions. And increasingly ,  
10 particularly companies in particular and in our own  
11 research with NIH grants, we give out very, very clear  
12 instructions on what to do and how to do it.

13 And I think one of the reasons that  
14 homogeneity becomes so important in really pivotal  
15 trials is that, and this is going to sound fluffy .  
16 But, there are people who love to heal wounds. And  
17 there are people who can't stand to look at them. And  
18 there are people who cannot stand chronic wounds  
19 because the people are -- I mean, I work in a VA  
20 hospital and I will tell you, impeccable cleanliness  
21 is not a high score. So, I mean, some people would  
22 not want to work with those patients.

23 And yet, I will tell you that because of  
24 the relationship that we establish with those patients  
25 because they know us, they know we're there, they know

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 that we're very serious about what we're doing, w e  
2 have minimal problems with compliance. And I thin k  
3 that's -- I think that could be echoed by numerous ke y  
4 centers in the country which I could identify in a  
5 nanosecond.

6 And the problem is when you go into a n  
7 area where somebody has all of a sudden decided that  
8 wound healing is vogueish, they haven't done clinical  
9 trials. They don't know how to take photographs .  
10 They don't know how to really measure wounds, e t  
11 cetera. I think that's where the patient begins t o  
12 sense that it's not important for him to be in this.  
13 And so, I see compliance as so mething, though I can't  
14 measure it at this point, I know it happens in ou r  
15 setting.

16 DOCTOR LAVIN: Yes, but yours is an ideal  
17 setting.

18 DOCTOR COOPER: Yes, but if we're going t o  
19 study wound healing products, one of the bigges t  
20 dilemma is that if we don't do it well, we can't get  
21 on about saying anything becau se we have a mush. And  
22 that's what we keep having. We have little trials ,  
23 not well done, not replicated in other parts of th e  
24 country. And consequently, we can't go forward at an y  
25 kind of an accelerated pace.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 CHAIRMAN MCGUIRE: Doctor Bergfeld.

2 DOCTOR BERGFELD: I'd like to just add to  
3 that comment that part of the variability has to do  
4 with training the centers and training the dedicated  
5 personnel that are in those centers who are going to  
6 care for the patients as well as instructing the  
7 patients. Without that training and without  
8 monitoring the training, and the compliance to  
9 training, these studies will fail.

10 CHAIRMAN MCGUIRE: Doctor Hashimoto.

11 DOCTOR HASHIMOTO: I suggest that later on  
12 the administration organize some study group and fund  
13 it. The VA has a good system. We can make the  
14 patient as free as before. Right now, the IRB  
15 prohibit admission of this kind of patient in the  
16 regular hospital beds but the VA still allows us to do  
17 so. I think that's probably the best organized study,  
18 compliance wise, we can supervise very well, qualified  
19 physicians. And that the national study, large  
20 group, probably can come up with meaningful data.

21 CHAIRMAN MCGUIRE: Yes, Doctor Lipsky and  
22 then I'm about ready to go on to the second part of  
23 the topic.

24 DOCTOR LIPSKY: I'd like to look at  
25 another aspect of compliance which is that I agree

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 with all the previous discussion of how critical it  
2 is. The FDA appears to look at safety and efficacy.  
3 I think if a new product came along that was no safer ,  
4 or no less safe and no less efficacious than another  
5 product, but was much easier for the patient to apply ,  
6 once daily versus four times a day, or much easier to  
7 put this on or a wound dressing that a patient or his  
8 family could do, that should be a substantial  
9 consideration as to whether that product should be  
10 approved.

11 CHAIRMAN MCGUIRE: I'm ready -- That's a  
12 very good point. Thanks for making it.

13 I'm about to read another paragraph .  
14 We're still under topic 1, standard of care, paragraph  
15 2.

16 "Many aspects of wound care are widely  
17 accepted in clinical practice. These include  
18 debridement to remove necrotic tissue, infection  
19 control, maintenance of a moist wound environment ,  
20 meeting nutritional requirements, and avoidance of  
21 topical and systemic cytotoxic agents. With regard to  
22 specific ulcer types, there is a general consensus for  
23 offloading and pressure relief of neuropathic and  
24 pressure ulcers, and for standard compression for  
25 venous stasis ulcers. However, there are no uniform

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 standards of care because strong evidence for specific  
2 standards is limited and the range of reported  
3 outcomes is variable, standard of care issues present  
4 a significant problem in the design of clinical trials  
5 for wound products."

6 Question. Which aspects of care should be  
7 standardized and to what extent for each arm in a  
8 clinical trial?

9 Anyone can address that. We've been  
10 talking about -- we've been talking about this but  
11 let's have more discussion on it.

12 Doctor Thomas.

13 DOCTOR THOMAS: I'll kick it off by saying  
14 this. For each of those issues, particularly in  
15 pressure ulcers, there -- it's very difficult to get  
16 any standard because they aren't real good standards.  
17 For example, for nutrition, we could argue about how  
18 do you -- how would you measure that in a clinical  
19 population? Whether you'd use albumin or whether  
20 you'd use some other instrument. Offloading of  
21 pressure is something that ought to be done but  
22 exactly how you do that is not clear.

23 So, you've really got two choices. One is  
24 that you can design your trials to be large enough to  
25 be able to analyze for these co-founders -- confounder

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 variables in the studies, or you can just set up some  
2 arbitrary system that allows you to do that. But for  
3 pressure ulcers, for examples, where most of the work  
4 is done in home or in nursing home long term care  
5 rather than hospitals for the reasons we've talked  
6 about, the patient variability and the frailty of that  
7 population, and the number of coexisting problems and  
8 illnesses make it almost impossible to adjust for all  
9 of the confounders.

10 So, while some things would be fairly  
11 simply, I think what you're going to have to do is  
12 take this approach we've already talked about. And  
13 that is, each of these ulcer categories are different  
14 and for each one, there are certain things that we can  
15 address and certain things that we can't address. We  
16 ought to address the things that we can and reach some  
17 consensus on them, and come up with some principles  
18 under each of those headings. And then for the things  
19 we can't adjust for, we're just going to have to  
20 adjust for that by a covaried analysis.

21 CHAIRMAN MCGUIRE: That was a very good  
22 statement.

23 Yes.

24 DOCTOR COOPER: Well, I took -- I tried to  
25 take three of the -- of each category of wounds and

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 begin to make some list of what the standardized - -  
2 standardization of care is, at least that I think has  
3 been sort of in a realm of a continuum discussed i n  
4 many trials that I've been in. And some of those wer e  
5 that -- I mean, we heard some of these yesterday, for  
6 the venous trial, that you have to have ankle brachia l  
7 indices.

8 And as someone else has said, you have to  
9 have some assessment of the vascular status, however  
10 you do that. I think you have to have TPCO2. I thin k  
11 you have to have compression. I think you have t o  
12 have tissue biopsy for bacterial status initially .  
13 I'm not so certain that you have to have it at the en d  
14 for the discussion that was already presented. I  
15 think you need to have whenever possible a standardiz e  
16 way and clarity on how you're going to measure th e  
17 area of this wound, even if you don't have digitized  
18 planimetry, I think that then the whole group has to  
19 know which area they're using as their tracing. Like  
20 the leading epithelial edge of a gnarled border. I  
21 think you have to establish recurrence rates so that  
22 you have to watch things over time. In cytosin e  
23 studies, it becomes increasingly important to see if  
24 we have any kind of regeneration so that we can, a t  
25 least in some of our studies, document that up to two

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 and a half years later these people have not had a  
2 venous ulcer in between because they have been  
3 compliant or in their compression, et cetera. Well,  
4 that's extremely significant.

5 Those were just some of the ones I came up  
6 for the venous ulcer.

7 CHAIRMAN MCGUIRE: And Ms. Cooper, that's  
8 very helpful.

9 Are there other statements?

10 DOCTOR THOMAS: If I could just respond  
11 briefly to that. I think it's a good list but it's  
12 illustrative of what we're talking about. Because I  
13 think if we went around and just sat down and talked  
14 about just that list on that category of ulcers, we'd  
15 probably have some wide ranges of agreement and  
16 disagreement.

17 DOCTOR COOPER: But I thought that's why  
18 we're here.

19 DOCTOR THOMAS: Well, I mean, yes, but  
20 what I'm suggesting is if we could take each category,  
21 go through each of those things that you talked about,  
22 and probably I'm not sure we'd reach a consensus even  
23 on that short list. I think you're going to have to  
24 build that. You're going to have to start the  
25 process. And if that's what we want to do, then we

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 could go through each of those and argue about them.  
2 But we'd have to do that for each category of ulcer.

3 In other words, I think it's a lot -- it' s  
4 just a hugely complex subject and what -- like biopsy  
5 by itself would be controversial. Some people would  
6 think that that was strongly indicated, some not. So ,  
7 if that's what we need to do, then if that's what we  
8 want to do, then we can certainly do that. W e  
9 certainly got experts here to talk about that.

10 DOCTOR COOPER: But it seems to me wha t  
11 the FDA is asking us that if we don't start -- I'm no t  
12 saying sit here all day and go over every singl e  
13 possible thing, but at least to give som e  
14 prioritization. Then they're no better off tha n  
15 before we came because it's in the literature. Bu t  
16 which ones do experts think ab out it. I guess that's  
17 -- I empathize with their dilemma.

18 DOCTOR THOMAS: Yes. It's a b ig problem.

19 CHAIRMAN MCGUIRE: Doctor Lips ky and then  
20 Doctor --

21 DOCTOR LIPSKY: I'd like to make on e  
22 general comment and then maybe a specific commen t  
23 about what Doctor Cooper has said. You asked Doctor  
24 Miller , Doctor McGuire, if he could come up with a  
25 standard for one type of wound and he responded o n

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 diabetic foot. I can tell you that the American  
2 Diabetes Association foot council, of which I'm a  
3 member, has recently done this. And we just met in  
4 Boston a couple of weeks ago and in a room larger than  
5 this with many more people. There was a lot of  
6 disagreement but we eventually were able to come up --  
7 and this process has been going on actually for  
8 several years -- with a list of things that we thought  
9 most people could agree on as long as there was some  
10 wiggle room for how one interpreted how to do that  
11 particular thing. So, we could agree on debridement  
12 even though there might be different techniques for  
13 doing it.

14 So, I think it is possible but it's very  
15 difficult and very time consuming, as you've heard  
16 from other speakers.

17 Just to address the issues that Doctor  
18 Cooper raised. I have less experience with venous  
19 ulcers than diabetic foot ulcers, but from the  
20 infection control point of view, I don't think that  
21 biopsies are necessary. In the best of all worlds,  
22 they are a good way of being certain that the  
23 organisms you grow actually represent organisms that  
24 are infecting deep tissues. And in several studies in  
25 the diabetic foot it has been shown that tissue biopsies

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 doesn't correlate or reverse that. That superficial  
2 cultures don't correlate very well with deep tissue  
3 biopsies. However, it's very difficult to get people  
4 to do that in clinical practice. It's even difficult  
5 to get investigators to do it correctly. The  
6 microbiology lab absolutely hates getting those kinds  
7 of specimens. And I think that there's sufficient  
8 data with the diabetic foot from three studies that  
9 show that cleansing the wound and scraping the base  
10 with either a tissue curette or just a scalpel, and  
11 sending that tissue down immediately to the  
12 microbiology lab is at least adequate when compared  
13 with biopsy specimens and much easier to do.

14 CHAIRMAN MCGUIRE: Doctor Margolis.

15 DOCTOR MARGOLIS: Some of what I was going  
16 to mention was just mentioned by Doctor Lipsky. I  
17 mean, I think in terms of generalities, we could  
18 probably come to some sort of consensus for a lot of  
19 points. People have already mentioned for venous leg  
20 ulcers they would use compression. For diabetic foot  
21 ulcers they would use offloading. For diabetic foot  
22 ulcers, debridement is important.

23 I think for some generalities we could  
24 probably do okay but for specifics like using TPCO  
25 for a venous leg ulcer or biopsies for venous leg

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1       ulcers, I think we'd have a harder time.     Bu t  
2       certainly I think we could make a   first cut or a firs t  
3       description in generalities.

4               The second point I wanted to address was  
5       also something that Doctor Cooper was betting into ,  
6       had to do with recurrence or r   ecidivism of venous leg  
7       ulcers, and that being an impo rtant part, perhaps, of  
8       also the initial assessment or maybe an idea o f  
9       compliance.   And I agree those sorts of issues ar e  
10      very important.   In some ways   they're more end points  
11     than what we're discussing.   And part of the reaso n  
12     for mentioning that is that I think end points ar e  
13     very tied into a lot of what we're now discussing as  
14     well.   To save end points for one of the las t  
15     discussions of the day I think seems a little bi t  
16     inappropriate and it might be worthwhile trying t o  
17     move it up because I have a feeling people are going  
18     to be thinking about end point s as they're discussing  
19     setting up standard of care and all sorts of othe r  
20     things in trial designs.

21              CHAIRMAN McGUIRE:   I said a few minute s  
22     ago that I think we could probably create differen t  
23     menus for different types of u lcers.   And there would  
24     be agreement, a general agreement, on the   top three or  
25     the top four, and then there would be som e

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 disagreement. And then there would be chaos beyond  
2 that level.

3 But I think you put it very well, Doctor  
4 Margolis, that there are some things we can agree on.  
5 And I think this is what the agency wants from us. In  
6 fact, I think the important thing, the important thing  
7 is that we make a clear distinction between the types  
8 of ulcers that we're dealing with. The complexity,  
9 the difficulty of dealing with these, probably varies.  
10 I think the chronic pressure ulcer, I mean, take the  
11 worse case. Take the spinal cord injury with a  
12 chronic pressure ulcer, this is going to recur,  
13 probably even in a facility where the individual is  
14 being taken care of full-time. And then we go on to  
15 the -- what now turns out to be a rather simple  
16 clinical event such as an arterial occlusion and you  
17 just -- it becomes a rather straightforward plumbing  
18 process. You get a very good result that has great  
19 durability.

20 But that's -- your points are well taken.

21 Doctor Miller to my left, you had a --

22 DOCTOR CLINTON MILLER: I would like to go  
23 back and perhaps ask the FDA exactly what their  
24 objective is in this question. The way I perceived it  
25 is that you're trying to describe a standard of care

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 as a matrix within which an experimental design can be  
2 constructed. If that's in case the objective, then it  
3 seems to me that the notion of care, say, for example,  
4 nutrition control or principle of offloading, or some  
5 other basic principles that need to be taken into  
6 consideration in the design of the clinical trial is  
7 the question. Can we make a list of those concepts,  
8 not necessarily how you're going to do it but the  
9 concepts that they would like to see built into the  
10 design of that experiment. And if that's what they're  
11 looking for, I do think we could sit down and talk  
12 about those principles as leave the individual hows to  
13 those people that are proposing a product or a  
14 treatment regiment.

15 CHAIRMAN MCGUIRE: I think we're moving  
16 very close to the third piece of this under topic one  
17 which is to define a program of care that represents  
18 current best clinical practice for each ulcer type.

19 DOCTOR MARZELLA: May I make a comment,  
20 Mr. Chairman?

21 CHAIRMAN MCGUIRE: Surely.

22 DOCTOR MARZELLA: I just wanted to respond  
23 to Doctor Miller's question and also indicate that  
24 what the agency is looking for is not only for an  
25 exhaustive list of standards, but also to sort of draw

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the line at which are critical to incorporate in the  
2 clinical trial design because there are  
3 practicabilities that we hear from sponsors regarding  
4 the ability to recruit centers, to recruit  
5 investigators. So, we are looking for standards that  
6 most investigators would consider acceptable and we  
7 would like to see where the committee feels the line  
8 would be for incorporating these criteria in the  
9 clinical trial.

10 CHAIRMAN MCGUIRE: Doctor Marzella, do you  
11 think it would be useful to go through this list of  
12 the A through F?

13 DOCTOR MARZELLA: Yes.

14 CHAIRMAN MCGUIRE: Please help define a  
15 program of care that represents current best clinical  
16 practice for each ulcer type and which would be  
17 appropriate for use in a clinical trial. Please  
18 address.

19 I'm pleased to see that drying with  
20 incandescent light is not on here. That's a great  
21 advance. The -- I didn't mean that as a joke, either.

22 (A) Methods for compression load pressure  
23 management. Well, that's really -- that's a lot of  
24 different things.

25 Yes, Doctor Thomas.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DOCTOR THOMAS: I'll start with pressure  
2 ulcers because that's what I deal with and somebod y  
3 else can deal with the other stuff. The problems tha t  
4 you get into with designing clinical trials for a  
5 pressure ulcer and offloading is the fact that tha t  
6 adds an enormous amount of expense to the trial. If  
7 you're going to use a standardized bed surface for th e  
8 control and experimental group, then you get int o  
9 enormous complexities in long term care because th e  
10 sponsor either has to provide that surface. There's  
11 no way if you're using multiple facilities that yo u  
12 can come up with a multiple facility single standard  
13 because of contract arrangements and third part y  
14 payers, and just huge amounts of difficulty. So ,  
15 that's one of the major difficulties.

16 There should be some offloading. Wha t  
17 we've done in our clinical tri als is we found that in  
18 most of our facilities for stage 3 and stage 4 ulcers ,  
19 that about 75 to 90 percent of the patients ar e  
20 offloaded. And so, we adjust for that as a confounde r  
21 to avoid the difficulty of hav ing to go in and try to  
22 set up some sort of standard offloading device .  
23 Because there's not good data in the literature t o  
24 suggest that one device is better than the other s o  
25 the least you can get is just equality between th e

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 groups for offloading.

2 CHAIRMAN MCGUIRE: Excuse me. So that I'm  
3 clear on this. We're talking about trochanteri c  
4 ulcers, sacral ulcers?

5 DOCTOR THOMAS: Yes, the pressure .  
6 Pressure, etiology, ulcers, for some bed surface o r  
7 for some offloading surface.

8 CHAIRMAN MCGUIRE: Because we're usin g  
9 offloading for the neuropathic ulcer, too.

10 DOCTOR THOMAS: Well, I'm addr essing just  
11 the pressure. I think the same thing would apply to  
12 each individual type of ulcer but I'm jus t  
13 illustrating this in terms of pressure ulcers and the  
14 difficulty that you run into in terms of doing that.

15 CHAIRMAN MCGUIRE: Do you have -- Could I  
16 ask you a technical question? Do you have techniques ,  
17 or practical techniques, for measuring shear injury i n  
18 your pressure ulcer patients?

19 DOCTOR THOMAS: No. Nobody reall y  
20 understands what shear is. No body really can define,  
21 except some mathematical models, exactly how i t  
22 interacts with pressure which is perpendicular an d  
23 shear which is horizontal. And it's then looked a t  
24 experimentally. And there's some really nice article s  
25 to give you some idea of what happens. But there's n o

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 clinical way to measuring it.

2           What we do is try to minimize the  
3 elevation of the head of the bed and that essentially  
4 will take care of some of the shear forces. And then  
5 we try to minimize friction forces which is the other  
6 component. And we try to build that into our trials  
7 and we also try to treat that as a confounder .  
8 Because if you have a tube feeder whose head of the  
9 bed is elevated, that person has shear forces whereas  
10 someone who is supine doesn't necessarily.

11           So it gets to be really complex but  
12 there's no -- the answer is no.

13           CHAIRMAN MCGUIRE:       And, are there  
14 practical ways to measure pressure?

15           DOCTOR THOMAS:   Practical, no. Ways to  
16 measure pressure, yes.       There's a considerable  
17 variability in how you measure pressure.   There -- the  
18 number of techniques and how that works. There are  
19 some pads, some bioengineered devices, that will  
20 measure interface pressures.   The variability and the  
21 reproducibility of that has been pretty poor so far.  
22 I think you can measure sitting pressures in  
23 wheelchairs.

24           There's a lot of great work that's been  
25 done on that. But as far as taking that into the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 field and incorporating that as part of a clinical  
2 trial, it would take biomedical engineers to do that.  
3 And you can't do that in the settings that we use. A  
4 lot of our patients are in home care for the reasons  
5 of discharge from hospitals. We can't study any  
6 pressure ulcer in a hospital because the patient is  
7 not there long enough. So, you're dealing with wounds  
8 that heal over 90 to 365 days. It has to be done in  
9 a setting that doesn't lend itself to that.

10 CHAIRMAN MCGUIRE: One thing that has not  
11 come up thus far is compression. And, would anyone  
12 like to take that on?

13 DOCTOR MUSTOE: I can take a stab at it,  
14 but not in a definitive way.

15 I think that the pressure sores are sort  
16 of unique in the expense of offloading. I still think  
17 that even in home care there are probably things that  
18 you could do such as overlays for beds that may be  
19 established in some standards 100 pound weight what kind  
20 of -- some -- I think that if you don't try to -- put  
21 on some standard, then you've sort of given up. I  
22 think in venous ulcers, it's much easier because the  
23 cost is much less. And I think there are lots of  
24 standardized compression garments around that are  
25 applied in standardized ways. And I think there

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 question is still is one better than the other. And  
2 I don't think that's been proven but I think in th e  
3 same study it's relatively easy to get the sam e  
4 device.

5 I guess I would say, though, t hat the key  
6 issue with compression is the absence of edema. And  
7 you can measure that and there probably could b e  
8 better ways to measure that than right now. We al l  
9 know what pitting edema is and we can measur e  
10 circumference, but there may be better ways out there .  
11 And I still think that that's an issue that -- The ke y  
12 issue is not the type of compression but have yo u  
13 achieved absence of edema. And if you have, the n  
14 you've got a very successful compression garment.

15 CHAIRMAN MCGUIRE: Doctor Marzella, di d  
16 you intend for us to talk abou t perforator competence  
17 and Doppler studies, and such things?

18 CHAIRMAN MCGUIRE: Yes, I thin k that that  
19 would be helpful.

20 DOCTOR ROSENBERG: Can I take a crack at  
21 that, Joe, about compression?

22 CHAIRMAN MCGUIRE: yes.

23 DOCTOR ROSENBERG: I think those of u s  
24 that have experience with this or that go to meetings  
25 and hear people who devote themselves to thi s

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 seriously. Terence Ryan at Ox ford and Chip Burdon at  
2 Duke, all come with this same feeling. And that is,  
3 if one understands that the problem is the edema and  
4 the return, and so forth, and if one applies  
5 compression, then these things heal. And that's about  
6 all there is to it.

7 And if one were to -- Doctor Mindel had  
8 mentioned. Maybe if we're trying to see an agent try  
9 and do it by itself, at least in terms of the venous  
10 ulcer, that's not real world. If the venous ulcer  
11 gets adequate compression, you can't stop it from  
12 healing. It heals very quickly. It doesn't need an  
13 agent to encourage it. If you don't, it won't heal.  
14 So, to think about products for venous ulcers without  
15 adequate compression I think is nonsensical.

16 And even more than that, even if one could  
17 heal it in bed with an agent, just our own experience  
18 at our own VA hospital, when explicit versus implicit  
19 audit was introduced as a way of auditing hospital  
20 care, one of course wanted to audit diseases that one  
21 dealt with. And we checked our VA census and the  
22 number one cause for bed days was leg ulcers. And we  
23 looked into it and go around to deciding that  
24 everybody -- we would put them in the hospital, they'd  
25 heal, and then they would be back in three months.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1                   And we started treating them    the Unna Boo t  
2    type technology and we found that when    we treated the m  
3    with Unna Boot technology, if they kept it up, the    y  
4    didn't come back.    And then we went the next ste p  
5    which others said that if you use Unna Boo t  
6    technology, you never need to put them    in the hospita l  
7    in the first place.    And now we go months without    a  
8    patient with leg ulcers at our hospital.

9                   So that the compression is the answer to  
10   leg ulcers and everything else is extraneous and --

11                   CHAIRMAN McGUIRE:   Bill --

12                   DOCTOR ROSENBERG:   I think products ar e  
13   just distraction.

14                   CHAIRMAN McGUIRE:   Thank you.

15                   You somehow slipped over to surgica l  
16   aspects of dealing with venous ulcers which    I  
17   recognize is not something that's likely to come t o  
18   this committee.    But many of us think tha t  
19   identification of incompetent perforators an d  
20   appropriate treatment is quite helpful and increases  
21   the durability of the result.

22                   Doctor Bergfeld, did you have a comment?

23                   DOCTOR BERGFELD:   Well, I was going t o  
24   come back to some of the basics which incorporat e  
25   questions 2 and 3.   As I sit here, I think that th e

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 basics for all of the wound types would include wound  
2 cleansing, infection control, debridement, mild or  
3 aggressive and some wet dressing. And then you've  
4 moved on to being specific about very specific ulcers  
5 and their etiologies. And under this tree, one has  
6 talked about also pressure compression and extensive  
7 debridement. And the other category that's been  
8 discussed in a general way is the general medical  
9 health of the individual, disease related, and control  
10 of disease in nutrition. And then the fourth category  
11 would be prevention.

12 I think that we could possibly agree on  
13 the basics and the four groups that I discussed,  
14 again, wound cleansing, infection control,  
15 debridement, and dressing. And where we are right now  
16 is in the arms of the specific type of ulcer and  
17 etiology of that ulcer, and discussing, then, the  
18 specifics under that type of ulceration.

19 CHAIRMAN MCGUIRE: Do you want to start  
20 with that?

21 DOCTOR BERGFELD: Well, I think you've  
22 already started. You've heard about pressure ulcers  
23 and offloading is common to both the diabetic as well  
24 as the pressure ulcer. In the venous ulcer, you have  
25 dealt with pressure which is the reverse, or

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 compression, and possibly surgical intervention. One  
2 might say that surgical intervention might be  
3 considered for all ulcers and discuss that, and  
4 discuss the parameters of that. And offloading,  
5 specifically on ulcers on pressure spots might be  
6 common to all ulcers.

7 CHAIRMAN MCGUIRE: Do you care to move on  
8 to debridement? We heard a lot about debridement  
9 yesterday from Doctor Miller.

10 Doctor Thomas, would you like to say  
11 something about debridement and pressure ulcers?

12 DOCTOR THOMAS: Yes. In terms of pressure  
13 ulcers, I think the standard is that the wound has to  
14 be clean, has to be debrided, prior to the start of  
15 the study. And that's currently what we do. We don't  
16 -- There's usually little need to do extensive  
17 debridement after the wound is clean, so we remove  
18 eschar, remove tissue, do that during a washing  
19 period, and then start active and control treatment  
20 arms.

21 And it's rare that we would have to  
22 debride the wound in any subsequent to that, and we  
23 would consider that a wound needing debridement after  
24 initial preparation to probably be a wound that's  
25 failing or worsening and we would drop that patient

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 from the study.

2 CHAIRMAN McGUIRE: Doctor Miller, o n  
3 average, how frequently would you debride a  
4 neuropathic ulcer?

5 DOCTOR FRED MILLER: I think this questio n  
6 came up yesterday when we looked at the study of the  
7 frequency of debridement and the question came up what  
8 type of debridement was carried out. I would agre e  
9 with Doctor Thomas that it's an initial debridemen t  
10 which is adequate. And then after that, there' s  
11 really very little debridement required unless there' s  
12 an advancing problem or you get callus which indicate s  
13 in the neuropathic ulcer there's some pressure and you  
14 might want to debride the callus.

15 But the initial debridement should b e  
16 adequate on these ulcers.

17 DOCTOR THOMAS: But if you debrid e  
18 subsequent for a neuropathic u lcer, that shouldn't be  
19 a reason to drop the patient. Whereas in pressur e  
20 ulcers, we find that it usually is.

21 DOCTOR FRED MILLER: Yes, that's right .  
22 Not necessary.

23 DOCTOR THOMAS: You want to clear that?

24 DOCTOR FRED MILLER: Yes.

25 DOCTOR COOPER: Doctor McGuire?

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 CHAIRMAN MCGUIRE: Would someone -- Yes?

2 DOCTOR COOPER: I was just going to ask - -

3 CHAIRMAN MCGUIRE: Ms. Cooper.

4 DOCTOR COOPER: -- Doctor Thomas --

5 DOCTOR THOMAS: I'm sorry. You better  
6 restate that. Excuse me.

7 DOCTOR COOPER: Excuse me. Doctor Thomas ,  
8 if you were to make suggestions in a pressure ulcer  
9 trial, would you also say that undermining needed to  
10 be removed?

11 DOCTOR THOMAS: Well, everything is  
12 controversial. So, I can tell you what I think but I  
13 also recognize that there are differences of opinion  
14 about that. My own personal bias is in the clinical  
15 treatment that I do of pressure ulcers, we rarely  
16 saucerize the ulcer. And we find that that usually is  
17 not necessary. And because of the type of dressings  
18 that we use and study and some of the newer types of  
19 dressing, we see that as not being an impediment to  
20 wound healing. So, we don't have to do that most of  
21 the time. And there are a lot of reasons for that.

22 Now, as I say this, let me distinguish in  
23 pressure ulcers two distinct populations. And that's  
24 the spinal cord injury patient and the elderly patient  
25 who's in long term care. About 70 percent of these

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 ulcers are in elderly patients and the rest of th e  
2 ulcers are probably in spinal cord patients. Spinal  
3 cord patients and elderly patients are two different  
4 groups.

5 Now, in spinal cord patients, I thin k  
6 there's a lot more of that done and it may be a lot - -  
7 and there may be more necessity for that being done.  
8 But for elderly patients, we run into problems tha t  
9 any time we do a surgical procedure lik e  
10 saucerization, we have difficulty because of the co-  
11 morbidities in that patient getting the patient t o  
12 heal. Secondly, there is, unfortunately, a lot o f  
13 ageism and age bias, and a lot of the patients can't  
14 consent to surgery or won't consent to surgery an d  
15 their caregivers say let's don't put them throug h  
16 anything. So, opportunities to do saucerization, or  
17 flaps, or things like that, are limited.

18 So, what we've done in common clinica l  
19 practice is to treat the wound and we've found tha t  
20 that's not really a problem. I probably -- I've had  
21 one patient I guess two weeks ago that I reall y  
22 thought I was going to have to do that. Th e  
23 indications for doing that are if the wound edge s  
24 become very rolled and callus and don't have an y  
25 epithelial margin, and all of this is subjective, to

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the point that you don't think that edge is going to  
2 respond or that the epithelium is growing under th e  
3 undermining. And if that is occurring, then I think  
4 it's something that has to be considered.

5 So, complicated answer. There 's a lot of  
6 debate about that. My own personal bias is that w e  
7 don't saucerize the ulcer as a routine.

8 DOCTOR COOPER: But getting back t o  
9 clinical trials, if you were to enter patients int o  
10 clinical trials that were stage 3 and 4 pressur e  
11 ulcers, I guess my concern is if you don't saucerize  
12 those ulcers, it's very, very difficult, then, t o  
13 compare them on center, the measurement, because o f  
14 the inability to measure volume, length and width ,  
15 area, et cetera.

16 DOCTOR THOMAS: I grant you that is one o f  
17 the real problems that we have and we have ways o f  
18 doing that. One of the exclusion criteria that we us e  
19 is undermining more than a centimeter. And if we hav e  
20 patients who do that, we usually don't enroll the m  
21 into a clinical trial for that reason.

22 Now, in the real world, which I try t o  
23 make our studies, because we're doing them in clinica l  
24 setting and I know what goes o n out there clinically,  
25 we try to deal with the situation as much ass we can

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the way that it's being dealt with in the real world.  
2 And in the real world, those wounds would not b e  
3 saucerized in elderly patients . And so therefore, we  
4 would not want to make that pa rt of the trial because  
5 then we would not be able to evaluate those -- w e  
6 would not be able to generaliz e those patients out to  
7 the larger population.

8 CHAIRMAN McGUIRE: Doctor Cooper, doe s  
9 that answer your --

10 DOCTOR COOPER: Yes, except that I think  
11 in certain specialties, a wound that was undermine d  
12 would always be saucerized, and plastic surgery.

13 DOCTOR THOMAS: And if you ask a barber i f  
14 you need a haircut -- I'm sorry.

15 DOCTOR COOPER: I don't know what tha t  
16 means.

17 CHAIRMAN McGUIRE: Well, that's anothe r  
18 way of saying if you go to an otolaryngologist, yo u  
19 usually get a tonsillectomy.

20 DOCTOR COOPER: I know. Well, but th e  
21 point is a lot of those people do studies is what I'm  
22 trying to --

23 DOCTOR THOMAS: And again, I emphasiz e  
24 that this is my opinion. I'm not a surgeon. I tend  
25 to deal with it that way. And my colleagues ,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 particularly in plastic surgery, would disagree  
2 vehemently with what I'm saying and would feel like  
3 that a wound always needed to be saucerized.

4 I can tell you that unless you are dealing  
5 with the wound center that has plastic surgeons as  
6 part of the team, most wounds, the general wounds, the  
7 pressure ulcers that in long term care, are not  
8 saucerized. They're treated with the undermining,  
9 with packing, and all that sort of stuff.

10 So again, it's controversial. There is  
11 disagreement about it. But I would suggest that the  
12 most common way of dealing with that problem, i.e.,  
13 the standard, is probably not to saucerize.

14 CHAIRMAN MCGUIRE: Doctor Rosenberg, would  
15 you care to comment on debridement in venous stasis  
16 ulcers?

17 DOCTOR ROSENBERG: I heard a really  
18 excellent talk recently by Doctor Burdon who has,  
19 really, more experience than we do in that. And he  
20 made the point explicitly that it really wasn't  
21 necessary. It cleaned itself up. You put the  
22 pressure on and under a moist dressing perhaps, and he  
23 said don't let anybody culture it because they'll  
24 panic. And he said it comes back next week. It's  
25 clean. And then you just go from there.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1                   Very impressive young man.    Recommend.  He  
2   has this clinic at Duke apparently when he was    a  
3   resident somebody said we ought to do something with  
4   leg ulcers and he was elected.  And he now does it   ,  
5   apparently, almost full-time.  And he's very good at  
6   it and he's very impressive.  Very impressive talk   .  
7   He's written some papers.

8                   And his own Unna Boot practice i s  
9   different from ours.  We're in the  -- We've actually- -  
10   I heard the talk and changed.  He says it's muc h  
11   easier to do.  There's little skill in applying th e  
12   Unna Boot to how much pressure.  And they don' t  
13   stretch all that well.  And as suming that the leg has  
14   been so that there's no edema in it, I mean, if yo u  
15   can get the patient off of it long enough to get the  
16   edema out, or else you're frequently applying the n  
17   until you get down to that state.  He puts the Unn a  
18   Boot, a premade Unna Boot, on without pressure, just  
19   smooth.  And then he uses a coband, a 3M self-adheren t  
20   sort of paper dressing, a full stretch.  He knows how  
21   many millimeters that is.  App lies it over top of the  
22   Unna Boot.  It sticks to itself but it doesn't stick  
23   to the Unna Boot.  And that's what he calls the Duke  
24   Boot.  And he --

25                   CHAIRMAN McGUIRE:  To be fair, a lot of u s

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 call it the Duke Boot.

2 DOCTOR ROSENBERG: Anyway, it was new to  
3 me, the coband over the Unna Boot. And he's ver y  
4 explicit about don't debride them, don't culture them .

5 CHAIRMAN MCGUIRE: I should point out tha t  
6 there is still a fair amount o f debridement going out  
7 out there in venous stasis ulcers. But I think Docto r  
8 Burdon is one of the better treaters in that area.

9 Could we talk about wound clea nsing, talk  
10 about different agents?

11 DOCTOR LIPSKY: Have we finishe d  
12 debridement, then?

13 CHAIRMAN MCGUIRE: Probably not.

14 Yes, Doctor Miller.

15 DOCTOR FRED MILLER: I think Bil l  
16 Rosenberg's comments illustrates getting back to basi c  
17 principles again. When we're talking about venou s  
18 ulcers , the sine quo non of therapy is compression .  
19 And then after that there are co-variants. How much  
20 debridement you have to do with venous ulcers, I thin k  
21 Skip Burdon has showed very well that if you use -- i f  
22 you do his Duke Boot with the hydrocolloid beneath th e  
23 Unna Boot, that you get autolysis and breakdown, and  
24 frequently you don't have to do mechanica l  
25 debridement. There will be a stasis ulcer where you

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 will have to do debridement depending upon the size  
2 and the extent of it.

3 But I think this is one of the variables,  
4 the debridement with the venous ulcers. But the sine  
5 quo non is you need the compression and how do you  
6 achieve that effectively? Can you do it with the Unna  
7 Boot and the coband, and that's the way that most of  
8 us do it, that's the basic therapy. And then after  
9 that, do we use a hydrocolloid, do we use an alginate  
10 beneath it. How do we approach the ulcer in addition  
11 to the compression.

12 CHAIRMAN McGUIRE: Doctor Lipsky, your  
13 questions suggest that you want to continue talking  
14 about debridement?

15 DOCTOR LIPSKY: Well, we've talked about  
16 a number of things, the need for debridement. I have  
17 a couple of other issues that might be worth raising.  
18 One is, do we need to do initial debridement that's  
19 total debridement? Doctor Miller showed yesterday a  
20 fairly aggressive approach and those who are skilled  
21 in doing that certainly can do it. Some people do a  
22 partial approach. They take off eschar, full  
23 thickness dead tissue. They certainly clean up  
24 anything that looks necrotic or infected and do some  
25 paring down of the ulcer. But at each visit, reassess

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 what needs to be done and then do further debridement .

2 So, I think I'd be interested in hearing  
3 from others about whether we have to -- whether th e  
4 suggestion should be a very aggressive initia l  
5 debridement with the belief, a t least in the diabetic  
6 foot infection, diabetic foot ulcer, that repeate d  
7 debridements are usually not necessary unless th e  
8 patient is not complying with the prescribe d  
9 treatment.

10 CHAIRMAN MCGUIRE: Well, you've -- Tom ,  
11 just a minute.

12 Fred, you've responded to that before. D o  
13 you want to say it again?

14 DOCTOR FRED MILLER: Again, I think that  
15 the amount of debridement, again, will depend upon the  
16 lesions. Venous ulcers --

17 CHAIRMAN MCGUIRE: I don't know if you r  
18 mike is live.

19 DOCTOR FRED MILLER: Is this live?

20 The venous ulcers, the debridement would  
21 be very variable. And again, it would depend upon th e  
22 situation. I think with the neuropathic ulcers ,  
23 especially one like I showed you yesterday with th e  
24 toe where you have bony seques terment, you have to be  
25 aggressive. You have to get r id of all that necrotic

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 material, all of those sequesters, or you will not  
2 heal the wound.

3 So, in my experience with the neuropathic  
4 ulcers, we are aggressive and thorough in our initial  
5 debridement. Venous ulcers vary.

6 CHAIRMAN MCGUIRE: Doctor Mustoe.

7 DOCTOR MUSTOE: I guess as a surgeon, I  
8 think the debridement, there's a bit of a continuum  
9 between debridement and cleansing. And I think that  
10 the reason why diabetic ulcers need debridement and  
11 respond so well is that you've got callus that harbor  
12 bacteria. You've got the diabetic who where the  
13 granulation tissue may be somewhat poorly perfused and  
14 you in some sense need to cut back to a totally clean  
15 and well perfused wound. And then you convert the  
16 situation.

17 In a venous ulcer, that's not the  
18 situation. The only reason debride I think that's  
19 been convincingly showed even though there's  
20 differences of opinions would be if there's necrotic  
21 tissue. And most of the time that will respond to  
22 vigorous cleansing if your cleansing is vigorous  
23 enough. And I would say the same thing goes for  
24 pressure sores, that unless there's necrotic tissue,  
25 there's no underlying basis for debridement because of

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 blood supply. You don't have this need to convert it  
2 to an acute wound. So, I think that the reason for  
3 debridement has to be looked at cleansing it must be  
4 acknowledge, is if it's aggressive enough, will  
5 effectively clean anything that's not -- doesn't have  
6 very tough collagen network holding the tissue down  
7 already.

8 CHAIRMAN MCGUIRE: Doctor Mustoe, I think  
9 you gave me the segue that I was looking for.

10 Debridement is a subset of wound  
11 cleansing. And I'm in wound cleansing now. And wound  
12 cleansing is controversial. A number of the things  
13 we've used with good intentions have been destructive  
14 to keratinocytes and have impaired epithelialization.

15 Doctor Thomas, you had your hand up.

16 DOCTOR THOMAS: Well, I was just going to  
17 say what you said. I think from the purposes of the  
18 FDA and the study, the wound cleansing should be as  
19 benign as possible unless, which means saline, unless  
20 there's some reason that it's part of the treatment or  
21 part of the evaluation. Because there's so many  
22 different wound cleansers that are toxic to wounds,  
23 then I think that becomes a compounder.

24 So, if there is going to be any wound  
25 cleansing with anything that is not absolutely benign,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 it has to be done in both arms. And I think if you do  
2 that, you'll be okay.

3 CHAIRMAN MCGUIRE: There's a lot of  
4 peroxide being used out there.

5 The hydrotherapy, which is not  
6 specifically listed here, is an important part of  
7 wound therapy and that ranges anywhere from a small  
8 whirlpool to a Hubbard tank. And I'm sure that in  
9 some of your pressure wounds, you use those heavily.

10 DOCTOR THOMAS: We do, and we use it for  
11 cleansing. Again, there's -- it's controversial .  
12 There's some bias. We just -- Rita France just did a  
13 review of that. It will be coming out in August.

14 There's a lot of controversy about  
15 whirlpools as to whether or not it's effective ,  
16 whether it's damaging, or whether or not it introduces  
17 more infection because of the problems with cleansing  
18 the tank and all that sort of stuff. But, it is used  
19 widely and it does tend to get debris out of a wound.  
20 So, it's six of one, half dozen of the other. You  
21 just-- but as long as you're doing the same thing in  
22 both arms, then you're okay on that. If somebody  
23 believes strongly that a wound has to be whirlpooled,  
24 what I don't want to see is the experimental arm for  
25 some reason all got whirlpooled and the control arm

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 didn't.

2 CHAIRMAN MCGUIRE: Yes.

3 DOCTOR SIMMONS-O'BRIEN: One of the things  
4 I wanted to say which gets back to compliance. In  
5 terms of wound cleansing, I think we need to make  
6 certain the patient has adequate pain control. Many--  
7 often times, even just with venous ulcers, a patient  
8 is in a lot of pain. And we can tell them how it  
9 should be cleaned and even cleanse it ourselves with  
10 not seeing adequately all of their grimacing during  
11 the visit. And they will not do any of this at home  
12 if it's painful. So, I think we should always address  
13 that and make sure that they have adequate pain  
14 control in order to do what they need to do.

15 And then, in addition to cleansing, I  
16 agree with Doctor Thomas. I think that we should go  
17 more of a benign route and also pay close attention to  
18 what else is going on with the skin surrounding that  
19 ulcer. Specifically, many of the patients with stasis  
20 ulcers will have horrendous eczematous dermatitis  
21 around that that area as well as maybe  
22 dermatolyosclerosis. And I think that you have to  
23 address the other cutaneous conditions surrounding the  
24 ulcer in terms of your cleansing, your cleansing  
25 technique and how, I guess eventually we'll segue into

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 dressing, that you've adequately taken care of th e  
2 other skin surrounding the ulcer.

3 CHAIRMAN McGUIRE: Yes, those wer e  
4 important points and thank you for bringing them up.  
5 Some of that eczematous dermatitis is contac t  
6 dermatitis, and especially in the chronic venou s  
7 stasis ulcers contact dermatitis is a part of it. And  
8 it's going to confound any study.

9 Anything more about --

10 Yes?

11 DOCTOR COOPER: I would just like to say  
12 that --

13 CHAIRMAN McGUIRE: It's Doctor Cooper.

14 DOCTOR COOPER: -- I think wound cleansin g  
15 is important but I don't think it needs -- and again,  
16 I think the specifics of it maybe shouldn't b e  
17 included in that. Because these patients ar e  
18 outpatients, using normal saline is enormou sl y  
19 expensive and most of our patients that are i n  
20 clinical trials go about their daily work, tak e  
21 showers, whatever. I mean, they wash their wounds of f  
22 with tap water.

23 So, I think to put increasing costs o n  
24 patients when they wouldn't do those things and that' s  
25 outpatient, we might not want to add that in, bu t

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 rather, that cleansing is important. I think in the  
2 hospital setting there's enough literature to show  
3 that you need at least seven pounds per square inch to  
4 irrigate a wound and to use aseptic syringes or bulb  
5 syringes is a waste of time and money.

6 CHAIRMAN MCGUIRE: The -- I'd like to  
7 comment on that, just to show you how cheap you can  
8 be. We make up our own saline. It's not sterile.  
9 And I don't think it has to be sterile. And saline,  
10 something near isotonicity is less painful for some  
11 patients than water. So, we just add -- we add a  
12 little salt to the water.

13 Doctor Lipsky, you had a comment?

14 DOCTOR LIPSKY: Yes, I think it's worth  
15 being explicit about the lack of need for antiseptic  
16 solutions to cleanse these wounds. Dilute betadine,  
17 hydrogen peroxide, a variety of other agents,  
18 Phisoderm, and so on, are used. And I think there's  
19 no evidence that I'm aware of that they are necessary  
20 and as has already been commented, there's pretty good  
21 data to suggest that they are toxic to newly forming  
22 epithelial cells.

23 So, I think that unless a sponsor can  
24 convince the agency of the need for using a topical  
25 antiseptic that that should not generally be

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 necessary.

2 CHAIRMAN MCGUIRE: And I think Docto r  
3 Thomas ' point is the critical one which is whateve r  
4 technique for cleansing is used needs to be used i n  
5 both arms.

6 DOCTOR FRED MILLER: I'd just like t o  
7 comment on the wound cleansing. I think that wit h  
8 most of these wounds there's very little need fo r  
9 cleansing. Once your wound is clean and you've done  
10 your weekly dressing, you just reapply the dressing.  
11 If you'd had a hydrocolloid on and you have a lot of  
12 debris beneath it, that can be cleansed and you can d o  
13 that very effectively with one of the little hardware  
14 store spray bottles with physiologic saline.

15 But we do very little wound cleansing at  
16 all. We just find that it's not needed.

17 CHAIRMAN MCGUIRE: I think you're trying  
18 to lead me into dressings. Good.

19 Doctor Hashimoto.

20 DOCTOR HASHIMOTO: I think at times a  
21 venous stasis ulcer has a very pruritic surroundin g  
22 area. Patients scratch which may contribute t o  
23 aggravating ulceration or creating new skin defects.  
24 Sometimes we use even 3M salin e injection surrounding  
25 the wound which relieves some of the fibrosis. An d

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 so, cortical steroids has some place in the care o f  
2 venous ulcers.

3 CHAIRMAN McGUIRE: Can we move t o  
4 dressings?

5 MS. COHEN: Break?

6 CHAIRMAN McGUIRE: No, we're going t o  
7 finish this and then break.

8 There is an enormous specification o f  
9 dressings. And one could go t o the hydrocolloid area  
10 and pick out 18 or 20. So, I don't want to talk abou t  
11 specific products. That will take forever. But, if  
12 anyone would like to open the discussion abou t  
13 dressings, Doctor Miller, why don't we start with you .  
14 You've seen the neuropathic ulcer. You've debride d  
15 it. And you're not going to see the patient again fo r  
16 a week.

17 DOCTOR FRED MILLER: Using the neuropathi c  
18 ulcer as an example, you have to define and look very  
19 specifically at where the neuropathic ulcer i s  
20 located. And I think we saw that dilemma yesterda y  
21 where we had many, many ulcers and it was ver y  
22 difficult to tell where was each of these ulcer s  
23 located and how would the treatment vary for th e  
24 particular location. Which on es need to be offloaded  
25 and offloaded for a 24 hour period.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           Our approach is if initially we would  
2 debride the ulcer and after the ulcer is adequately  
3 debrided, then it's a matter of maintaining a moist  
4 wound environment. If it's an ulcer, we'll pack it  
5 and we'll usually be using just saline gauze. And  
6 that would be packed on a daily basis. Once the ulcer  
7 is clean, it doesn't have to be done more than once a  
8 day. If we're trying to maintain the moisture because  
9 we want it to be moist to moist as opposed to moist to  
10 dry because we already have a clean ulcer, we might  
11 even use Saran Wrap around it.

12           Now, we're talking, then, about an ulcer  
13 that might be on the toe or on the dorsal foot, or on  
14 the lateral foot where we can have relief of pressure.  
15 If the ulcer is over a metatarsal head or a heel, then  
16 we're probably going to go to a contact cast. And  
17 that ulcer will have an Unna Boot directly against the  
18 debrided ulcer followed by the plaster and then the  
19 glass cast. And that will be changed at a week and  
20 then reapplied. And then maybe allowed to be on for  
21 a two to three week period.

22           But once it's debrided, it's maintaining  
23 a moist environment. We don't tend to use the  
24 hydrocolloids on the diabetic feet the way we do on  
25 the venous ulcers. We tend to use saline more.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 CHAIRMAN MCGUIRE: Would anyone like t o  
2 comment on venous stasis ulcers?

3 Yes. It's Doctor Cooper.

4 DOCTOR COOPER: I think getting back t o  
5 what we're trying to do which is do clinical trials,  
6 one of the things that really important to do in the  
7 venous ulcer is to monitor its size, reduction in siz e  
8 over time, as well as the patient's compliance wit h  
9 compression hose. So, I would think that -- I would  
10 suggest that whatever kind of dressing is used, i t  
11 needs to either be changed once a day or twice i n  
12 clinical trials, especially in the beginning because  
13 there's high levels of proteasis which are ver y  
14 disruptive to healing.

15 CHAIRMAN MCGUIRE: Are there othe r  
16 comments on venous stasis ulcers?

17 Yes, Doctor Margolis.

18 DOCTOR MARGOLIS: I think with the venous  
19 leg ulcer, just as Doctor Miller and Doctor Coope r  
20 have been mentioning, it depends on the situation .  
21 The idea is to maintain a mois t environment. There's  
22 lots of dressings you can use. If your environment i s  
23 one where you're using a compression bandage for a  
24 venous leg ulcer that you're changing once a week ,  
25 you're of course going to use a different dressin g

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 than one that you're going to change every day. The  
2 idea behind it is to keep the wound moist and in a  
3 clinical trial, you'd want to have dressing types that  
4 are going to do that efficiently in both arms.

5 The difficulty for some of these things,  
6 especially with dressings in the settings that we're  
7 talking about, it's often the dressing is what's being  
8 studied. So, certainly you would want something in  
9 the control arm that also going to keep the wound  
10 moist and it's going to obviously be different then.

11 CHAIRMAN MCGUIRE: I think the other  
12 important point here is -- Or, I think it's a n  
13 important point, is that with the venous stasis ulcer  
14 you need to wait until the wound is stabilized. I n  
15 other words, you need -- once you've put on a n  
16 occlusive dressing, you need to check that at a rather  
17 short interval to make sure th at things are going the  
18 way you want them. That is, if there's bee n  
19 ortholysis, that the debris is being removed, and that  
20 you haven't become clinically infected. After yo u  
21 achieve some wound stability, then you can go into a  
22 weekly dressing change.

23 But there -- I mention that because in th e  
24 -- if you were doing trials on venous stasis ulcers,  
25 the first week or two weeks is going to be different

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 than the chronic phase peeling.

2 Doctor Miller, did you have a comment?

3 DOCTOR CLINTON MILLER: I just want t o  
4 make the observation that it seems to me that th e  
5 principle here is consistency in the arms. There are  
6 essentially -- we made a list not too long ago o f  
7 dressings and it was over 200 different dressings .  
8 And so, we're not talking about practice. We'r e  
9 talking about the design of a clinical trial an d  
10 consistency is the issue.

11 CHAIRMAN MCGUIRE: Yes, and without -- I  
12 hope without offending any of the industry, there' s  
13 been an enormous amount of mimicry in the dressings.  
14 And if you find one dressing, you can find six mor e  
15 pretty much like it.

16 Any more on dressings? Surgic al closure.  
17 Who would like to comment on surgical closure?

18 DOCTOR MUSTOE: I guess I could as a  
19 surgeon. I think that the pressure sore -- I thin k  
20 surgical closure is an area that probably even mor e  
21 than, or at least every bit as much as any other area ,  
22 there's no studies to support long term benefits o f  
23 surgical closure so it's still an open issue.

24 I think there's no question th at surgical  
25 closure -- I think all surgeon s would accept that you

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 can't close a surgical wound until it's clean. Bu t  
2 the issue is that when do you close a pressure sore o r  
3 when do you put a skin graft on. And I don't thin k  
4 that at the moment there is a consensus. So, I think  
5 it's very tough to develop guidelines to say when it' s  
6 appropriate.

7 CHAIRMAN McGUIRE: Yes, Doctor Harkless.

8 DOCTOR HARKLESS: On diabetic ulcers, I  
9 think that they all heal with appropriate offloading  
10 and debridement that Doctor Miller has already allude d  
11 to. So, I don't think you need to surgically excise  
12 the ulcer. It usually will heal with offloading. An d  
13 if it doesn't respond then you may need surgery t o  
14 alleviate or take out the meta tarsal head in terms of  
15 a resection.

16 CHAIRMAN McGUIRE: It's not strictl y  
17 speaking surgery but there are a number of device s  
18 available now for promoting wound closure. And I' m  
19 not expert in that area.

20 If there's nothing -- Yes, Doctor Lavin.

21 DOCTOR LAVIN: My only comment on surgica l  
22 closure is that in a study whe re you are placing some  
23 type of a graft material over the wound and looking a t  
24 time to healing, were one to be doing surgica l  
25 closure, that would represent a failure in the study.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 So, one needs to just make sure that that and other  
2 analytic complexities get addressed by doing such  
3 extra things.

4 CHAIRMAN MCGUIRE: Can we go to  
5 antimicrobials? Who would like to comment on  
6 antimicrobials? And we're talking -- here the issue  
7 is systemic antimicrobials.

8 Yes? Doctor Thomas.

9 DOCTOR THOMAS: I don't think that we --  
10 and I don't want to get off the subject, but if we  
11 need to go back and talk about choices of dressings  
12 and pressure ulcers because we didn't do that?

13 CHAIRMAN MCGUIRE: We can go back.

14 DOCTOR THOMAS: At some point.

15 CHAIRMAN MCGUIRE: Let's do it now, then.

16 DOCTOR THOMAS: You want to do now.

17 The problem with design of the clinical  
18 trials in pressure ulcers is that you've got two  
19 complexities. One is that different stages of  
20 different treatments, and when you combine them all  
21 together it's difficult to find one control arm  
22 dressing that meets all of those criteria.

23 For example, the standard of care probably  
24 is normal saline to compare to. But what we do, and  
25 I think we need to make some improvements in the way

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 we do those control arms, is that if we're looking at  
2 a control arm, we need to look at what the dressing,  
3 the treatment arm, is designed to do. And if the  
4 treatment arm is designed to do a specific thing, then  
5 we need to mimic that.

6 And the other dilemma that I think exists  
7 is that occlusive dressings for pressure ulcers have  
8 now been shown to be superior to saline. And so, for  
9 some trials and some ulcers it may not be appropriate  
10 to compare those to historical controls or to saline  
11 controls. And so, we've run into the dilemma of  
12 whether we're going to compare a new treatment to a  
13 saline which has been considered the gold standard, or  
14 to some other type of occlusive dressing that may have  
15 been shown to have acceleration of healing over the  
16 saline controls.

17 So, it gets to be a real problem in terms  
18 of design. And I would love to hear what the rest of  
19 the panel thinks in terms of a control dressing for  
20 pressure ulcers.

21 CHAIRMAN MCGUIRE: You're talking about a  
22 control dressing within a current study or comparing  
23 it with historical studies?

24 DOCTOR THOMAS: No, control arm for a  
25 treatment dressing. You want to look at Product X for

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the treatment of stage 3 and 4 ulcers.

2 CHAIRMAN MCGUIRE: I think there's genera l  
3 concern about comparing a current treatment wit h  
4 historical treatment.

5 Would anyone like to comment on that?

6 Doctor Cooper.

7 DOCTOR COOPER: We use normal saline and  
8 gauze, historic, the same historical.

9 DOCTOR LIPSKY: One of the things tha t  
10 I've observed that industry so metimes does is if they  
11 are looking down the road of pricing and they come ou t  
12 equivalent to another dressing, they're going to try  
13 to choose a dressing that's at a higher price. So, I  
14 don't think that should be the consideration tha t  
15 should be used for determining what the control ar m  
16 should receive.

17 DOCTOR THOMAS: Well, my concern is that  
18 to some extent what we do in general practice ,  
19 clinical practice, is that we use -- the dressing tha t  
20 I use for particular ulcers may not be normal saline  
21 and I'm becoming a little more hesitant to make that  
22 my control arm, which I think is one of the issues th e  
23 agency has to look at.

24 What am I -- Am I going to compare this to  
25 what I think the best treatment is or am I going t o

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 compare this to what I think the gold standard has  
2 been. And that's a dilemma and I don't know the  
3 answer.

4 Sorry to get off the track.

5 DOCTOR CLINTON MILLER: It's a little bit  
6 off the topic right now. I would like to speak just  
7 briefly to the danger of embracing arm designs. And  
8 I think this point that you're raising is to which of  
9 those arms should and should not have alternative  
10 dressings that clarifies the issue. And that is these  
11 arm designs often wind up kind of like an octopus.  
12 You just have arms all over the place and subarms.  
13 And the problem is in those designs you're unable to  
14 estimate interaction effects. And that is a very  
15 powerful argument against an arm design.

16 Almost, I would say almost always, you're  
17 trying to find out how a treatment and the  
18 alternatives are going to interact with each other.  
19 How multiple factors interact to obtain an optimal  
20 effect. When you do that, you've got to measure  
21 interaction and you cannot do that with arm designs.  
22 So, I think you ought to be very cautious as a general  
23 principle in accepting that approach to the design of  
24 these trials.

25 CHAIRMAN MCGUIRE: Can we revisit

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1       microbials, antimicrobials?

2                   DOCTOR HARKLESS:  Doctor McGuire, were yo  u  
3       alluding to topical or systemic antimicrobial?

4                   CHAIRMAN MCGUIRE:  I think we're talking  
5       about systemic antimicrobials at this point.

6                   Doctor Cooper.

7                   DOCTOR COOPER:  I think there's evidence  
8       from Robson, Kruzek, Heggars, and others, tha  t  
9       systemic antibiotics do not ge  t into a chronic wound.  
10      And I think in the presence of cellulitis, systemi  c  
11      antibiotics can be used as a treatment and I thin  k  
12      that that should not be an exclusionary criteria for  
13      a patient in a study since this has been norma  l  
14      historical evolution of some of these wounds  at times .

15                  CHAIRMAN MCGUIRE:  Doctor Lipsky.

16                  DOCTOR LIPSKY:  I think the first thing w  e  
17      have to do is to define infect  ion in each study.  So,  
18      in chronic wounds it can be ve  ry difficult to define.  
19      The presence of organisms is universal and therefore  
20      certainly is not a definition of infection.  Infectio  n  
21      probably needs to be defined clinically rather tha  n  
22      microbiologically.  Once you clinically believe that  
23      the wound is infected, you culture it to determin  e  
24      what organisms are causing the infection and wha  t  
25      their antimicrobial susceptibilities are so you ca  n

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 choose the best antibiotic agent, at least for you r  
2 definitive if not your empiric therapy.

3 The definition that we have used and has  
4 been increasingly adopted, I think, in diabetic foot  
5 trials, anyway, is the presence of either purulence o r  
6 two or more signs of inflammation. If there's pus ,  
7 the body thinks the wound is infected and I'll tak e  
8 its word for that. If there's two or more signs o f  
9 inflammation and there's no other reason for that, I  
10 think that's a reasonable alternative definition for  
11 infection.

12 If the wound is infected --

13 CHAIRMAN McGUIRE: Excuse me. You'r e  
14 talking about neuropathic ulcers?

15 DOCTOR LIPSKY: That's correct.

16 If the wound is infected, the n  
17 antimicrobial therapy is necessary. We hav e  
18 traditionally used systemic antimicrobial therapy ,  
19 particularly in the presence of, say, more than just  
20 a rim of cellulitis because that's what works .  
21 Topical antimicrobial therapy is just recently being  
22 relooked at. So, to stick with the systemi c  
23 antibiotic therapy, I think if there's an infection,  
24 that would probably be the standard of treating it.

25 The question that Doctor Cooper raise s

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 about penetration of antibiotics, this has been  
2 heavily debated in many areas in infectious diseases.  
3 For example, osteomyelitis where for many years we  
4 looked at bone levels and Carl Nordon and others who  
5 have done the most work in this have abandoned that  
6 approach saying that we just don't know what to make  
7 of levels in many tissues.

8           There are three or four studies that I  
9 know of in diabetic foot neuropathic ulcers that have  
10 attempted to measure antimicrobial levels and they're  
11 wildly variable, even within individual centers. I  
12 think what we can say is that systemic antibiotic  
13 therapy seems to adequately treat most infections as  
14 long as you've debrided out any necrotic material.

15           Topical antimicrobials, unlike the  
16 comments that I made about topical antiseptics, are  
17 generally benign on the wounds as opposed to being  
18 toxic to newly forming epithelial cells. Whether or  
19 not they're effective in treating mildly infected  
20 diabetic neuropathic ulcers is not known. There's at  
21 least one trial that's been completed that looked at  
22 a topical antimicrobial compared with a systemic  
23 antimicrobial that I've been associated with. But,  
24 there are very few studies that looked at the efficacy  
25 of topical antimicrobials for treating infected

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 wounds.

2 Now, if you move on to non-infected  
3 wounds, then the issue becomes is either systemic or  
4 topical antimicrobial therapy indicated, and I think  
5 that's an area that's open to debate and that's  
6 largely because there aren't any good studies. There  
7 are only a few studies. The ones that I know of are  
8 actually mostly in abstract form. They never seem to  
9 get published. That suggests that antimicrobial  
10 therapy either does or does not, depending upon the  
11 study, benefit clinically uninfected wounds. I think  
12 in the absence of data suggesting that giving  
13 antimicrobials is helpful, we should default to the  
14 environmentally more defensible position of not  
15 scattering antibiotics on wounds that have not been  
16 proven to need them.

17 CHAIRMAN MCGUIRE: I would like to make  
18 one brief comment on venous stasis ulcers. And that  
19 is, when a stasis ulcer is -- has not changed for a  
20 while and rapidly deteriorates, that's often an  
21 indication of infection and the infection is often a  
22 streptococcal infection. And those ulcers do respond,  
23 or the inflammation, does respond to systemic  
24 antibiotics. But I think everyone knows that and  
25 that's a special case.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           Are there other comments on systemic - -  
2           Yes, Doctor Margolis.

3           DOCTOR MARGOLIS: I would also argue ,  
4           though, and this point was partially raised already,  
5           they can be very difficult finding clinical scienc e  
6           for venous leg ulcers to diagnosing infection i n  
7           surrounding erythomeas, either secondary to contac t  
8           dermatitis, or an irritant dermatitis, or t o  
9           dermatosclerosis. So, using clinical science ca n  
10          often be very, very difficult.

11          CHAIRMAN McGUIRE: But what you do an d  
12          what I do, when we see deterioration of a stasi s  
13          ulcer, is that we -- I usually culture and trea t  
14          simultaneously.

15          DOCTOR MARGOLIS: I do and I a lso look at  
16          the care the patient is receiving and wonder whether  
17          or not they really have good edema control. It' s  
18          often when I see -- in that setting, I'll see people  
19          who are all of a sudden developing leg edema eithe r  
20          because I haven't applied a bandage correctly, o r  
21          they're not compliant, or they 've removed the bandage  
22          or removed the stocking. Or there's anothe r  
23          concomitant medical problem.

24          CHAIRMAN McGUIRE: Yes, Doctor Thomas.

25          DOCTOR THOMAS: I'll just comment o n

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 pressure ulcers. Since most pressure ulcers are  
2 dealing with topical dressings and since when we're  
3 looking at that in the experimental arm, we're  
4 concerned about the possibility of creating infection  
5 or causing infection, then I think that if a pressure  
6 ulcer gets infected during a clinical trial, we  
7 usually drop that patient.

8 And we don't enroll patients who have  
9 obvious infections. And I agree that the treatment,  
10 then, is going to be topical although occasionally we  
11 do use systemic antibiotics. If we use systemic  
12 antibiotics, we think the patient is really ill or  
13 septic, and in that situation the patient should be  
14 dropped. And if we use a topical antibiotic, which I  
15 think you have to do, then it confounds the study to  
16 the point that the patient should be dropped.

17 So, for pressure ulcers, the use of  
18 antibiotics during the course of a clinical trial  
19 ought to be a reason to exclude the patient.

20 CHAIRMAN MCGUIRE: Thanks very much.

21 I would like to take a break at this  
22 point, and the rest of you are invited. And we will--  
23 I'd like to get back here a little bit after 11:00.

24 (Whereupon, the foregoing matter went off  
25 the record at 10:52 a.m. and back on the record at

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 11:12 a.m.)

2 CHAIRMAN MCGUIRE: Good mornin g. We have  
3 completed our discussion of topic 1 which turned out  
4 to be a little more complex than I anticipated. W e  
5 have topic 2, discontinuation of study treatment for  
6 adverse effects, blinding, and vehicle controls.

7 Topic 2 is divided into three pieces, to  
8 which I've added a fourth piece which I'll surpris e  
9 you with in a few minutes. Let me read the first par t  
10 of topic 2. And as I'm readin g this, think about the  
11 two questions that the agency has asked us t o  
12 consider.

13 First, "Please discuss the impact o f  
14 infection on the patient statu s in a clinical trial."  
15 And (B), "Under what circumsta nces should the patient  
16 be considered a treatment failure and removed fro m  
17 treatment once infection is diagnosed?"

18 The statement, "Infection is a commo n  
19 occurrence in non-healing ulcers. There is a wid e  
20 range of severity of infection, osteomyelitis an d  
21 septicemia are serious events in the presence of which  
22 a patient's experimental treatment in a clinical tria l  
23 is typically discontinued and the patient is followed  
24 up for resolution of the event. Cellulitis, a mor e  
25 common infection, is often treated with appropriat e

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 antimicrobials while the patient continues on th e  
2 experimental treatment."

3 "Use of an experimental agent migh t  
4 increase the risk or impair the resolution o f  
5 infection, therefore discontinuation of experimental  
6 therapy in patients who develop infections may b e  
7 advisable in some settings. However, infections are  
8 not common in chronic ulcers -- infections are no t  
9 uncommon in chronic ulcers and will occu r  
10 independently of experimental agents. The use o f  
11 experimental agents in the presence of infection migh t  
12 be desirable."

13 "Thus, discontinuation of patients wit h  
14 infections could lead to unnec essary loss of power in  
15 the study and to loss of information about the effect s  
16 of concomitant use of antimicrobial agents."

17 And then the two issues, "Please discuss  
18 the impact of infection on the patient's status in a  
19 clinical trial. And, (2), under what circumstance s  
20 should the patient be considered a treatment failure  
21 and removed from treatment once infection i s  
22 diagnosed?"

23 Who would like to step up to that?

24 Yes, Doctor Cooper.

25 DOCTOR COOPER: I think particularl y

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 speaking about the venous ulcer and the pressur e  
2 ulcer, if you don't know the bacterial status of the  
3 patient prior to them going into the study, tha t  
4 you're comparing apples and or anges. And so, I would  
5 say that the bacterial status of the wound has to be  
6 determined prior to entrance into the study.

7 CHAIRMAN McGUIRE: And by bacteria l  
8 status , you're -- you are not referring t o  
9 quantitative microbiology. You're talking -- you're  
10 referring to a culture?

11 DOCTOR COOPER: I am. I would refer back  
12 to quantitative bacteriology.

13 CHAIRMAN McGUIRE: So you'd do a biops y  
14 and culture the biopsy?

15 DOCTOR COOPER: Every patient in ou r  
16 clinical trials has a culture. And if they hav e  
17 greater than  $10^5$  or one beta strep, they're no t  
18 admitted into the study until that is resolved.

19 CHAIRMAN McGUIRE: Are there othe r  
20 comments?

21 DOCTOR LIPSKY: And what's been you r  
22 experience in terms of comparing? You don't pu t  
23 anybody in who has more than  $10^5$  so you don't hav e  
24 data, therefore, to allow you to know whether that wa s  
25 necessary. I mean, on what ba sis are you making that

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 decision?

2 DOCTOR COOPER: I believe -- Th e  
3 investigations that have been done prior to this b y  
4 Doctor Robson and others have shown that if you have  
5 a wound that's infected by that definition, it's a  
6 different behaving wound. And so, at least -- I mean ,  
7 if you've got every other variable sort of controlled ,  
8 like, say, TCPO2 or size of the ulcer, or whatever ,  
9 and you ignore the bacterial status of the wound ,  
10 that's a major reason that the wound has not closed.

11 DOCTOR LIPSKY: I would just start b y  
12 making a plea that we be careful about use of the ter m  
13 infection. Based upon the comments that I mad e  
14 previously, I would say that what you're definin g  
15 there as bacterial burden, if you will, or microbial  
16 colonization levels, or any ot her term you might want  
17 to use, so that's the first point. That doing a  
18 biopsy and defining the number and types of organisms  
19 doesn't prove that the wound is infected. It jus t  
20 tells you the level of colonization of the wound.

21 A separate issue is, does that high level  
22 of colonization of the wound, be it  $10^5$ ,  $10^6$ , or  
23 whatever, correlate with failure of the wound to b e  
24 healed? And that's a controversial area. I thin k  
25 perhaps the best data is in burn wounds where biopsie s

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 of the burn wound with high levels of organisms show  
2 that you need to eradicate those organisms in orde r  
3 for the burn wound to heal. But when it comes t o  
4 other wounds, I think there's less data and the data  
5 are less consistent.

6 Doing quantitative microbiology ,  
7 particularly to return to the diabetic neuropathi c  
8 ulcer where most of my experience is, it's ver y  
9 difficult to get sufficient ti ssue to do quantitative  
10 microbiology. In one trial that we finally persuaded  
11 our micro lab to do it, they abandoned it because it  
12 was just so hard for them to actually quantify th e  
13 organisms. There's an average of four to fiv e  
14 different organisms per wound, each of which then has  
15 to be quantified. And then do you take the total of  
16 all of them or do you take the most pathogenic one, o r  
17 do you take the dominant one? I think you get into a  
18 very difficult microbial situation without strong dat a  
19 that I'm aware of. And I'd be interested to know if  
20 there's other data in other fields that I don't read  
21 as much to demonstrate that it's necessary.

22 CHAIRMAN McGUIRE: I think the original - -  
23 I would be pleased to be corre cted on this point, but  
24 I think the original study took place at least 2 0  
25 years ago and that's the one that Tom Krisek an d

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Robson did. And that was directed toward graft acceptance and the  $10^5$  --

3 DOCTOR LIPSKY: That's correct.

4 CHAIRMAN MCGUIRE: -- was the -- became that mythic number that we've all referred to since. But even the  $10^5$  was not accurate if you were dealing with strep, a very -- a much smaller number would prevent graft acceptance if you were dealing with streptococcal infection.

10 DOCTOR LIPSKY: I think with a particularly virulent organism like a beta hemolytic strep, that lower numbers of organisms would be pathogenic. Whereas, on the other hand, a relatively non-virulent organism like a coagulase negative staphylococcus or a bacillus species, even higher numbers probably don't, except in an otherwise immunocompromised patient, constitute concern for infection.

19 But, you're right, with closure of a wound by grafting or grafting of a burn wound, that's a surgical procedure where you would expect that having a decontaminated and certainly uninfected field would be important.

24 CHAIRMAN MCGUIRE: I would like for this discussion to go on and I think the danger is that

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 we'll become mired in the distinction between  
2 infection and colonization. And that's a difficult  
3 issue for me.

4 Ms. Cohen, you had a comment.

5 MS. COHEN: Yes, shouldn't a clinical  
6 trial be typical of what happens, and I submit it's  
7 just as important to find out why something doesn't  
8 work as well as it does work. And you have -- this is  
9 a complicated subject. It's, as you said, it's not  
10 taking two pills. It's much more than that. And I  
11 always wondered about the line below the graft, where  
12 things don't work, and why didn't it work? And could  
13 they learn from it and do better?

14 So, I just think could someone -- whatever  
15 you want to call it, infection or whatever it is, just  
16 to drop them to me is really anti-intellectual, to  
17 tell you the truth. It's like an easy way out and we  
18 don't have to think it through.

19 CHAIRMAN McGUIRE: Are there other  
20 comments?

21 Doctor Wilkin.

22 DOCTOR WILKIN: If I could have a  
23 clarification about the quantitative microbiology.  
24 Does the committee believe that there should be a  
25 quantitative microbiology? I'm aware of what Calvin

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Kunin did with bacterial infections of the bladder ,  
2 urinary tract infections. And there the organisms are  
3 fairly well mixed and there's homogeneity within the  
4 sampling volume. It seems in a wound site there is  
5 heterogeneity from one site to the next. If you look  
6 on biopsy, you see a cluster of organisms and then  
7 maybe a substantial field where you don't see  
8 anything. If there is a sense that we need  
9 quantitative microbiology, is there a technique where  
10 one could obtain quantitative microbiology? I'm not  
11 sure where  $10^5$  really came from in wound healing.

12 CHAIRMAN MCGUIRE: Well, we know where it  
13 came from in grafting.

14 Doctor Thomas.

15 DOCTOR THOMAS: This whole issue in terms  
16 of clinical trials gets real complicated. But I think  
17 the  $10^5$  is all in acute wounds. And there's no  
18 question acute wounds, graft wounds, burns, things  
19 like that, that that works out all right.

20 Quantitative microbiology is the best tool  
21 that we have to define the presence of bacterial in  
22 these wounds because they're colonized and surface  
23 contamination is not correlated with the quantitative  
24 wound biopsy.

25 So, it's the best of everything that we

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 have to measure bacteria. However, it's ver y  
2 difficult to correlate that with wound outcome. And  
3 there are some studies that Marty has done tha t  
4 suggest that but there's other data that suggests tha t  
5 that is confounded and all that.

6 From a practical standpoint, it' s  
7 impossible to get quantitative cultures because of th e  
8 necessity to do a biopsy and the reluctance of th e  
9 micro labs to do this, and the enormous expens e  
10 involved in doing it. I think that for pressur e  
11 ulcers, the diagnosis of infection is usually mad e  
12 clinically and we have descriptions that we use fo r  
13 our studies of clinical infection. Once a wound i s  
14 infected, it's going to requir e topical treatment and  
15 the topical treatment confounds the experiment. So,  
16 we drop patients for that reason.

17 If the patient requires systemati c  
18 antibiotics, then we think the patient is at risk of  
19 sepsis and we can't continue a treatment that may be  
20 contributing to that. So, that's the reason that we  
21 drop patients from that. So, I think that that shoul d  
22 be done in pressure ulcers.

23 Now, in diabetic ulcers, in ve nous stasis  
24 ulcers, my experience has been that those wound s  
25 frequently are infected during the course of treatmen t

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 and almost sort of expected. It just happens, th e  
2 longer you go, they may have t wo or three episodes of  
3 cellulitis. And so, I think t hose patients should be  
4 treated concurrently and that's not a reason to drop  
5 those patients.

6 CHAIRMAN McGUIRE: Doctor Wilkin, doe s  
7 that come close to answering you question?

8 DOCTOR WILKIN: Well, if I could restate  
9 part of his answer, is that practically we're no t  
10 going to attain biopsy which would be necessary.

11 DOCTOR THOMAS: It's practical, numbe r  
12 one, because we've done this in a couple of studies,  
13 and it's extremely difficult. It's been requested .  
14 We can't get it done and can't make any arrangements  
15 to get it done.

16 And then, secondly, in terms of what you  
17 were talking about, the question really is how wel l  
18 does that correlate with what' s going on in the wound  
19 and that data is very elusive. So, I think that -- I  
20 think it's practically impossible unless we're going  
21 to set up some mechanism to get it done, if we'r e  
22 going to require it. And seco ndly, I'm not sure that  
23 it's correlated with outcome in pressure ulcers.

24 CHAIRMAN McGUIRE: And the other side of  
25 that, Doctor Wilkin, is that Doctor Cooper considers

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 that a criterion for entry.

2 Yes, there's a question from the audience .

3 MR. BARBEAU: Adrian Barbeau, John s  
4 Hopkins. Just to answer your question. The  $10^5$  came  
5 from Robson and Krisek, and related to failure of skin  
6 grafts to take. And it was noted at  $10^5$  or greater  
7 that the skin grafts to take on a bed. And if there  
8 were less cultures in a tissue than that number, the  
9 grafts would take.

10 The application of that number to chronic  
11 wounds which are left open has no basis. And that's- -  
12 I think that's your question that you're answering ,  
13 where did that number come from. And it was in  
14 acutely applying skin grafts to ulcer beds.

15 DOCTOR LIPSKY: I would add there's on e  
16 other source that it comes from which is burn wound  
17 sepsis where when you have greater than  $10^5$  the  
18 chances of developing systemic sepsis from your wound  
19 is greater. And those are the only two instances ,  
20 your analogy to UTI aside, that there is evidence tha t  
21 quantitative microbe predicts an outcome, there isn't  
22 any good data to my knowledge in other kinds o f  
23 wounds.

24 CHAIRMAN MCGUIRE: Doctor Lavin.

25 DOCTOR LAVIN: Yes, I'd like to make a

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 point on clarification to something Doctor Thomas said  
2 a couple of comments ago about dropping patients due  
3 to infections. I think the proper way of looking at  
4 these studies is to always look at them as the primary  
5 analysis being intent to treat where all patients are  
6 included. Any such patient who would drop under those  
7 circumstance would be counted as a treatment failure.

8 I think the whole point is to include the  
9 experience from all of the patients in the study. And  
10 if you do have a treatment that induces a higher rate  
11 of infection, either accidentally or just  
12 purposefully, that situation should be reflected in  
13 the data and everyone should be counted.

14 CHAIRMAN McGUIRE: The second part -- I  
15 must say, the agency --

16 DOCTOR HARKLESS: Question for Doctor  
17 Lipsky from a neuropathic ulcer perspective. You  
18 mentioned that you had to have two signs of infection  
19 and purulence, is that what you said?

20 DOCTOR THOMAS: Either purulence alone or  
21 two or more signs of inflammation.

22 DOCTOR HARKLESS: I kind of have a problem  
23 with the two signs of inflammation because if you  
24 agree with Brand's work, you can have inflammation  
25 without infection and temperature will go up several

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 degrees without infection. So , you can have swelling  
2 and some redness on a neuropathic ulcer that may not  
3 be infected. And I see that all the time. I don' t  
4 know whether Doctor Miller will like to make a commen t  
5 on that?

6 DOCTOR LIPSKY: I agree except that I  
7 don't know how else to define. Do you have some othe r  
8 way that you can -- You're saying that they'r e  
9 infect ed and I presume that means that something i n  
10 your gut tells you that, or your experience, tells yo u  
11 that this is an infected wound.

12 DOCTOR HARKLESS: Well, I think th e  
13 duration of the ulceration probably has more of a role  
14 in that, how much they've walked. I agree tha t  
15 purulence is very, very important. But just to have  
16 some surrounding edema around an ulceration .  
17 Generally I'm not necessarily that concerned about it  
18 after I debride similar to what Doctor Mille r  
19 demonstrated yesterday.

20 DOCTOR LIPSKY: We're just fac ed with the  
21 problem that some wounds, there isn't purulence but by  
22 some clinical criteria we think that there are fiv e  
23 cardinal signs of inflammation. And if you've got a  
24 couple of them and you have no other obvious cause fo r  
25 inflammation, it's difficult to exclude infection.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 I agree with you that you can have  
2 inflammation in the absence of probably infection. I  
3 would just say in the neuropathic diabetic foot ulcer,  
4 that if you're -- if the therapy under consideration  
5 is a wound healing agent, that I would be comfortable  
6 allowing the patient to continue in the trial despite  
7 developing an apparent infection by whatever  
8 definition is agreed upon in advance. But that  
9 certainly needs to be noted because there may  
10 well be agents that increase the likelihood of  
11 infections developing. But I wouldn't use that as a  
12 reason to drop the person from the trial.

13 But they would have to be treated  
14 systemically.

15 CHAIRMAN MCGUIRE: Doctor Marzella, you  
16 have -- you've forced the advisory committee into a  
17 position where we were about to admit that we can't  
18 recognize infection.

19 DOCTOR THOMAS: Never.

20 CHAIRMAN MCGUIRE: I'm sure that's not  
21 what you meant to do. I'm sure you wanted an answer.  
22 And I think what we're dealing with is who's winning,  
23 the host or the organism. And in a well-run  
24 operation, the host wins and the organism may still be  
25 there. It can be there for years, but the host wins.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 And then the issue is when does the organism become  
2 more aggressive and put the host at risk, and then  
3 when do you drop that patient from a trial.

4 I think simply colonization -- what I'm  
5 hearing is that colonization would not direct you to  
6 that action, nor would treatment with a systemic  
7 antimicrobial.

8 Yes?

9 DOCTOR THOMAS: Pressure ulcers, I would  
10 say it would.

11 CHAIRMAN MCGUIRE: Pressure ulcer, if you  
12 needed to treat with a systemic antibiotic, you would  
13 drop?

14 DOCTOR THOMAS: Yes. Because I can't  
15 imagine a circumstance where you would administer a  
16 systemic antibiotic for a suspected infection in a  
17 pressure ulcer where you wouldn't also be obligated to  
18 give a topical treatment. And you can't put a topical  
19 treatment in an arm where you either have a control or  
20 another agent. So, by definition you violated the  
21 protocol and that patient has to be come out.

22 Now, you're right, it's intent to treat.  
23 And if you found that that happened to 18 experimental  
24 patients and only two control patients, then I would  
25 start really worrying.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 CHAIRMAN MCGUIRE: Sure. Doctor Weiss.

2 DOCTOR WEISS: I was wondering if I could  
3 ask a question to Doctor Thomas.

4 What -- Do you have any feeling for what  
5 is the expected incidents of individuals that would  
6 become infected and would have to drop out of a trial,  
7 because that would just have to obviously be included  
8 into your sample size calculations when you start the  
9 trial. I was just wondering.

10 DOCTOR THOMAS: Right. The incidents in  
11 infection is not known. We use some guesses and we  
12 guess somewhere in the neighborhood of five to ten  
13 percent. In fact, we rarely see an infection in these  
14 wounds because our inclusion/exclusion criteria  
15 usually for the study are going to exclude people that  
16 are likely to do that. And so, I would say we  
17 probably have not lost more than one percent to  
18 infection.

19 Now, our big problem is that we lose  
20 people to death. People die much more frequently in  
21 these trials and our death rate is somewhere around 10  
22 to 20 percent. And so, we have to build in those  
23 parameters in terms of sample size in order to take  
24 care of death. Infection is really not a problem in  
25 pressure ulcers.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 CHAIRMAN McGUIRE: Doctor Lavin.

2 DOCTOR LAVIN: Yes, just a point on follow  
3 up to something that Doctor Weiss said.

4 Basically I would definitely not adjust  
5 the sample size on the basis of expectation of numbers  
6 of -- of drop outs due to infection because they'd be  
7 treatment failures. I would adjust the sample size on  
8 the basis of losses of patients due to follow up or  
9 data that can't be used. There's a big distinction  
10 between those two things.

11 In a trial like this, my experience has  
12 been expect 20 percent of the population to be -- to  
13 not be useable for one reason or another, but not --  
14 But having an infection would make it a useable  
15 patient. It's the lost to follow up that you have to  
16 worry about without knowing why they were lost to  
17 follow up.

18 DOCTOR THOMAS: Good point.

19 CHAIRMAN McGUIRE: Doctor Bergfeld had a  
20 remark.

21 DOCTOR BERGFELD: Doctor Thomas, I just  
22 wanted to ask you a question about the topical use of  
23 antimicrobials in your pressure ulcerations and the  
24 exclusion criteria that you've applied.

25 If the patient is his or her own control

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 and you aren't working against controls, would there  
2 be an opportunity to use in the control ulceration the  
3 antimicrobial at the same time you're using it in the  
4 treated ulcer so that you would continue to have the  
5 patient treated in a similar manner. And the  
6 continue to keep the patient within the study group?

7 DOCTOR THOMAS: I got lost.

8 DOCTOR BERGFELD: Well, I'm trying to  
9 match your control with your ulceration. If you  
10 have--

11 DOCTOR THOMAS: I have an ulcer patient  
12 and control patient.

13 DOCTOR BERGFELD: You have two different  
14 patients, not two ulcers in one patients.

15 DOCTOR THOMAS: Two different patients and  
16 one of them gets an infection. And I'm going to use  
17 a topical antibiotic in that patient, whether it's  
18 control or experimental.

19 DOCTOR BERGFELD: Yes.

20 DOCTOR THOMAS: The problem that I have is  
21 if you look at studies in terms of wound accelerants,  
22 antibiotics, maybe because of a vehicle effect or  
23 maybe because of the antibiotic, and we can go into  
24 that and look at it. But, I mean, basically, things  
25 that have antibiotics in it have been shown to be

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 superior to placebo in wound healing. And the y  
2 accelerate wounds that heal anywhere from about 1 9  
3 percent up to about 25 percent acceleration of healing  
4 rates.

5 And so, if I use an agent that accelerate s  
6 the healing rate in either arm, then I've made a  
7 problem in terms of my analysis of outcome. An d  
8 that's my concern. I can't use an antibiotic in the  
9 wound that may not accelerate or have some effect on  
10 that wound. And so, if I have to stop my therapy in  
11 order to put an antibiotic in for ten days and tha t  
12 accelerates the healing curve for that wound, then I  
13 go back to my original control , then I've accelerated  
14 that wound in that arm. And I think that that would  
15 be a protocol violation. I do n't think I could get a  
16 good answer if I did that.

17 And if I think the wound's clinicall y  
18 infected, I've got to use a topical antibiotic. I  
19 can't rely on a systemic although I may use a  
20 systemic, along with it. So, I'm caught in a rea l  
21 quandary here and the only way I know to deal wit h  
22 that in pressure ulcers is to consider that a  
23 treatment failure.

24 CHAIRMAN McGUIRE: I think that's clear.

25 And I think that's one of the answers the agency i s

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 looking for.

2 The -- Yes, Tom.

3 DOCTOR MUSTOE: I just was going to say,  
4 if you think, though, that just to get back to you r  
5 alternative dressing, that if you feel tha t  
6 antimicrobials increase -- accelerate healing by 19 t o  
7 25 percent, by that analogy, you should use them i n  
8 every patient.

9 DOCTOR THOMAS: We can talk about that bu t  
10 actually, if you take the antibiotic, and there have  
11 been some studies that have done this. If you tak e  
12 the antibiotic and use exactly the same antibiotic in  
13 a petroleum-based vehicle and then you use it as a  
14 powder, it --t he powder has a negative effect.

15 And so, there aren't good studies tha t  
16 actually have done vehicle controls for this, so w e  
17 don't really know whether it's the antimicrobial o r  
18 whether or not it's the vehicl e control. And so, you  
19 may be in a situation where you're just simply using  
20 another kind of occlusive dressing.

21 CHAIRMAN McGUIRE: Speaker from the floor .

22 MR. CHERRY: George Cherry. A ny time you  
23 quote a figure like that, could you please tell - -  
24 give us some of the publication that topica l  
25 antibiotics can speedup the healing by percentage ?

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Because earlier, you said they didn't make an y  
2 difference in the healing, if I remember correctly .  
3 Did I hear you that in pressure sores?

4 DOCTOR THOMAS: No, you've not heard m e  
5 say that they didn't make any difference.

6 MR. CHERRY: But I think if you quot e  
7 figures like that.

8 DOCTOR THOMAS: All right. I wish that I  
9 could give you stuff like this off the top of my head ,  
10 but I will provide you with a reference.

11 CHAIRMAN McGUIRE: The agency has a  
12 question about evaluation of outcome by third part y  
13 when the study cannot be blinded. And it occurs to m e  
14 that some of the reasons that a study can't b e  
15 blinded, it's also not going to be blinded to th e  
16 third party, either, especially when we're dealin g  
17 with grafts and devices, and so forth.

18 But, let's see what we can do with that.

19 MS. COHEN: Doctor McGuire, I'm here. I' m  
20 still here. I haven't gone away.

21 CHAIRMAN McGUIRE: Ms. Cohen.

22 MS. COHEN: I never will. What are yo u  
23 going to do.

24 Doctor Thomas, I really don't understand  
25 something. As a would be pati ent, I'm brought into a

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 clinical trial and in the process I develop  
2 cellulitis. I develop a bacterial infection. It does  
3 prove that the treatment is not working, but why not  
4 continue. It's like an experiment in a lab, you don't  
5 give up because it doesn't work. You keep trying and  
6 you learn from it. And if that treatment doesn't  
7 work, you've learned it doesn't work because certain  
8 other things are happening. And I should think  
9 scientifically and intellectually you would want to  
10 know why and go on and see what you could do about it.

11 DOCTOR THOMAS: Now, I'm a little lost.  
12 You're going to have to walk me through this. You're  
13 a patient. You get -- you have a pressure ulcer. You  
14 develop an infection.

15 MS. COHEN: No, but I'm in the clinical  
16 trial.

17 DOCTOR THOMAS: You're in a clinical trial  
18 and you're getting a treatment.

19 MS. COHEN: Yes.

20 DOCTOR THOMAS: And this treatment is some  
21 sort of salve or something that's on your pressure  
22 ulcer?

23 MS. COHEN: Right.

24 DOCTOR THOMAS: Now, the problem that  
25 we've got is that if you get what I think is a

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 infection, my obligation is to treat that infection.  
2 So, now I have to use another agent.

3 MS. COHEN: I understand that. But --

4 DOCTOR THOMAS: So, am I going to put bot h  
5 agents in the wound?

6 MS. COHEN: If that's what it merits and  
7 that's what it dictates.

8 DOCTOR THOMAS: But see, the problem i s  
9 that I don't know what the interaction is going to be .  
10 I can't put two things in the same wound.

11 MS. COHEN: Then someone's going to have  
12 to treat the wound somewhere. So, if you don't do it ,  
13 someone else is going to do it.

14 DOCTOR THOMAS: No, I'm not saying don't  
15 treat the wound. What I'm saying is I have to shift  
16 to a different treatment.

17 MS. COHEN: Excuse me. Does that not tel l  
18 you that what was used at that time allowed something  
19 else to happen? And doesn't that provide you wit h  
20 information?

21 DOCTOR THOMAS: No. What that tells me i s  
22 that that patient in the course of --

23 MS. COHEN: Treatment.

24 DOCTOR THOMAS: -- these three months tha t  
25 I'm treating got an infection in a wound. It' s

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 common. It happens whether I'm treating or not. It  
2 may have been in the control arm. It may have been in  
3 the experimental arm. Now, when I get through with  
4 the trial, if it turns out that in the experimental  
5 arm that I've got 18 infections and in the control arm  
6 I've got two, then that would raise serious questions  
7 as to whether or not the treatment promoted infection.

8 MS. COHEN: Well, that's the point,

9 DOCTOR THOMAS: But, I'll know that. I'm  
10 going to collect that data and I'll know that. I will  
11 not lose that data. The only thing I can't tell is  
12 when that individual wound gets infected.

13 MS. COHEN: And then that person is  
14 dropped. They're not followed any longer in the  
15 trial. And then what happens? I think it would be  
16 intellectually very challenging to find out.

17 DOCTOR THOMAS: All right. Let's talk  
18 about dropped. I use that word and Doctor Lavin  
19 corrected me and that's true. When we're talking  
20 about dropped, it means that I have all the data from  
21 when we started up to that point. And that patient  
22 will be considered a treatment failure. It will go  
23 negatively against that agent. And when I say  
24 dropped, it doesn't mean kicked out of the nursing  
25 home or ignored, or something like that. It means

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 censored is what we use statistically. But tha t  
2 patient would be treated, then, appropriately wit h  
3 some other agent. It's just that I can't put t o  
4 things in the same wound.

5 MS. COHEN: Well, it seems --

6 DOCTOR THOMAS: You will find -- I mean,  
7 I promise -- I know I may not be explaining this very  
8 well --

9 MS. COHEN: No, you did. You explaine d  
10 it. I understood it.

11 DOCTOR THOMAS: But I'll know wha t  
12 happened to that patient and I will know that tha t  
13 patient was a treatment failure.

14 MS. COHEN: Well, it sounds like half an  
15 experiment to me, but that's the way I view it.

16 DOCTOR THOMAS: It really isn't.

17 MS. COHEN: Thank you.

18 CHAIRMAN McGUIRE: Are there othe r  
19 comments before we go on to the third part y  
20 evaluation?

21 Yes.

22 DOCTOR O'CONNELL: Doctor McGu ire, as far  
23 as discontinuation, I just wanted to clarify one thing  
24 that was mentioned earlier. I s there a difference in  
25 venous stasis versus decubitus, versus the neuropathi c

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1       ulcers in whether or not you d   iscontinue patients who  
2       need to be debrided as the tri   al is progressing? Not  
3       the initial debridement but th   e debridement after the  
4       experimental treatment has started?

5                   CHAIRMAN   McGUIRE:       You have a ver y  
6       definite answer from Doctor Thomas on pressure ulcers   .

7                   DOCTOR O'CONNELL:   Right.

8                   CHAIRMAN McGUIRE:   What do we hear about  
9       neuropathic ulcers?

10                  DOCTOR   FRED   MILLER:       So, what you'r e  
11       saying, Kathy, if you have to   repeat the debridement?

12                  DOCTOR O'CONNELL:   Right. After you'v e  
13       done the initial debridement and you've started th   e  
14       experimental   treatment, if the patient require s  
15       debridement again, do you cons   ider that a failure and  
16       discontinue the patient?

17                  DOCTOR FRED MILLER:   No, I wou ldn't think  
18       so. I think that initially you do that "thorough   "  
19       debridement and that's certain ly in quotes. And then  
20       you might have to do some lesser   debridement as you g o  
21       along. You might get some cal   lus formation and you'd  
22       have to distinguish that from actually debriding the  
23       wound itself.

24                  But you might   even have, let's say, a bon y  
25       shard in the wound that you didn't pick up initially

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 and then that becomes more apparent as you probe the  
2 wound and follow up. But no, I think you could do  
3 subsequent debridements.

4 But I think the point is the initial  
5 debridement should be thorough, as thorough as  
6 possible.

7 DOCTOR O'CONNELL: And then would you use  
8 that as a covariate when you analyze the data, whether  
9 the patient did require debridement as the trial went  
10 on?

11 DOCTOR FRED MILLER: I guess off the top  
12 of my head I would say no that would not -- I would be  
13 looking -- maybe the covariable would be the  
14 offloading, the efficacy of the offloading device  
15 because callus had formed. And where we're getting  
16 friction and pressure, and that required debridement.  
17 So that would be the variable as opposed to --

18 CHAIRMAN MCGUIRE: Let's hear from Doctor  
19 Lavin and then I would like to hear what Doctor Lipsky  
20 has to say.

21 DOCTOR LAVIN: Yes, just in terms of  
22 debridement, you wouldn't count that. You would count  
23 that essentially and you'd look at the incidents of  
24 debridement, or the mean number of debridements, in  
25 each of the two treatment groups. But you wouldn't

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 count that as a failure nor would you count that as a  
2 reason for going off study. So that would be counted .

3 And you could also count that and include  
4 that as an example of a time varying covariate which  
5 is something that may influence outcome. So, a  
6 patient who gets debridement may actually be going  
7 back to square one. Or, they may be getting some  
8 advantage. So, analytically that does have to be  
9 built into the modeling. And all of these analyses  
10 that we're doing here, we really have to be setting  
11 forth standards of how to properly analyze the data.

12 The data, no matter what, no matter what  
13 kind of ulcer you're looking at, it cuts across all  
14 ulcers. We're going to have to analyze these data  
15 with time varying Cox proportional hazards models .  
16 And it's a standard that I think will be inevitable  
17 for looking at all of these data. Not only are you  
18 going to have to look at baseline covariates like the  
19 size of the ulcer, the history of how long they've had  
20 the ulcer, the TCPO2, hemoglobin A1C. You're going to  
21 have to be looking at that. But these time varying  
22 covariates and you're also going to have to be paying  
23 the price of looking at center or I should say study  
24 by treatment interactions. And these are all the  
25 price that have to be paid to do these studies

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 properly.

2 CHAIRMAN MCGUIRE: Do you have anything to  
3 add, Doctor Lipsky?

4 DOCTOR LIPSKY: I agree with Doctor Lavin  
5 and just a couple of brief points.

6 One is I'm hard pressed to think of a  
7 reason why a topical wound healing agent would cause  
8 the need for more debridement although it's  
9 conceivable that if you put something that turned into  
10 concrete on the wound or that would need to be  
11 chiseled off, not to be too facetious about it. But  
12 there are agents, I suppose, that might increase the  
13 need for debridement.

14 The failure or the need to debride again  
15 probably more often than not represents failure to  
16 adequately debride at the beginning. So, it's sort of  
17 an investigator failure rather than an investigationa l  
18 agent failure.

19 So, I think you ought to be able to do it  
20 if you need to do it and that shouldn't be a reason  
21 for dropping.

22 CHAIRMAN MCGUIRE: Your question was  
23 directed towards all classes of ulcers and if I can  
24 just take a position on the stasis ulcer and then I'll  
25 see if the committee wants to change that or modify.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 I think with regard to stasis ulcers, at  
2 the outset one could identify the number of, fo r  
3 instance, the number of times one treated wit h  
4 systemic antibiotic. Stasis ulcers become infecte d  
5 with enough regularity that I think probably you would  
6 not want to remove all of those patients from th e  
7 study. But there probably sho uld be some limit. And  
8 that could be done arbitrarily but rather easily a t  
9 the outset of the study.

10 Would someone on the committee like t o  
11 change that or modify it?

12 It's hard to believe. The --

13 DOCTOR O'CONNELL: Thank you.

14 CHAIRMAN MCGUIRE: Now can we go to third  
15 party evaluation?

16 Would someone who's had experience wit h  
17 third party evaluation like to comment on this? Yes,  
18 Doctor Miller.

19 DOCTOR CLINTON MILLER: One of ou r  
20 speakers this morning had as one of their objectives  
21 the avoidance of third party assessment. And I wante d  
22 to shoot my arm up right quick and say someone tha t  
23 proposes avoidance of third party assessment basicall y  
24 doesn't believe in bias. The flat fact is we've got  
25 books written on about 195 different sources of bias

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 and one of the foremost and most frequently observed  
2 is an observer bias.

3 So, I would be very much opposed to avoid ,  
4 let's say not have third party assessment where it's  
5 possible.

6 Now, if you wanted to propose minimize the  
7 number of people making that third party assessment,  
8 I might buy that because frequently -- but I wouldn't  
9 want to do it to the point where the bias was  
10 compounded with center differences. In other words,  
11 like you had a project in a single center trial and  
12 all the assessments done by one person, then that  
13 person's bias would be compounded with the center  
14 differences. So, I would say that you could minimize  
15 third party assessors but you shouldn't avoid them  
16 from the point of view of just not having it done.

17 CHAIRMAN MCGUIRE: Are there other  
18 comments?

19 DOCTOR ROSENBERG: I would.

20 CHAIRMAN MCGUIRE: Yes, Doctor Rosenberg.

21 DOCTOR ROSENBERG: I think in cases of  
22 ulcers, it seems to me we can get objective evidence  
23 of healing with tracings, or photographs, or  
24 impressions, and so forth. I mean, the whole point  
25 about bias is that for areas that can't be measured

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 that objectively. But I would think that -- maybe  
2 not.

3 CHAIRMAN MCGUIRE: Well, I think here  
4 we're specifically --

5 DOCTOR CLINTON MILLER: You have a topic --

6 CHAIRMAN MCGUIRE: Excuse me. We're  
7 specifically talking about subjective criteria and  
8 you're pointing out that you'd like to stay away from  
9 subjective criteria. And I think everyone agrees with  
10 that. But at times you're going to be stuck with  
11 subjective criteria. The question is, can someone  
12 from down the hall evaluate your patient and do a  
13 better job than you can? And the point has been made  
14 that at times that will be essential but it's a risky  
15 business, too. It's not entirely safe.

16 DOCTOR CLINTON MILLER: We have another  
17 item on the agenda today that's going to talk about  
18 endpoints. And I think it depends upon the choice of  
19 endpoint we're talking about as to whether or not  
20 that's possible to be that objective.

21 CHAIRMAN MCGUIRE: Doctor Lavin.

22 DOCTOR LAVIN: My comment on this business  
23 of a third party evaluator, I think at a single site  
24 it's sometimes difficult to do because the burden of  
25 patients, the number of patients, may be so large ,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 their schedules may be so varied, so there really is  
2 a noblesse oblige to have one third party evaluato r  
3 there who will always be able to evaluate ever y  
4 patient in the study. And that's probably the mos t  
5 ideal way of dealing with it. And the next most idea l  
6 way is to have the same evaluator, there would b e  
7 multiple evaluators being there to evaluate always th e  
8 same patient.

9 So, those are the two things that ca n  
10 often times be -- go awry in these studies. Thir d  
11 party evaluators, there's nothing wrong with them .  
12 They do reduce bias. I agree with Clint in tha t  
13 respect. But they better be the same perso n  
14 evaluating the same patient.

15 CHAIRMAN MCGUIRE: I think I h ave a -- do  
16 you have a clear picture of where we're --

17 DOCTOR CLINTON MILLER: Thank you ver y  
18 much for that.

19 CHAIRMAN MCGUIRE: In vehicle controlled  
20 studies, this is the third part. In vehicl e  
21 controlled studies, demonstration of superiority o f  
22 the product to its vehicle may not establish clinical  
23 benefit if the effect of the v ehicle on wound healing  
24 is not known. For example, the combination of a n  
25 active ingredient in a toxic vehicle may out perform

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the vehicle alone yet may not be effective. Please  
2 discuss circumstances under which comparison of a  
3 experimental agent to standard care as well as vehicle  
4 is appropriate during the product development.

5 DOCTOR CLINTON MILLER: I'd make the  
6 observation that this question and its resolution are  
7 a product of the arm's design. If you have the three  
8 arms, what you're saying is that you have A, you have  
9 B, and you have AB, and those three arms. Without  
10 that control, you cannot look at those differences.  
11 And so this is the product that develops from  
12 accepting arm designs rather than factorial designs.

13 CHAIRMAN MCGUIRE: Doctor Hashimoto.

14 DOCTOR HASHIMOTO: I just wonder if this  
15 vehicle may stimulate release of the PDGF from any  
16 microphage or caratonocids, those endogenous source of  
17 PDGF? If that can be done as a control?

18 CHAIRMAN MCGUIRE: I think the question is  
19 can the vehicle itself be beneficial. Can it have a  
20 salutary effect on the wound and that has to be  
21 tested.

22 Are there other questions?

23 DOCTOR BERGFELD: I'm sorry. Are you  
24 saying that the test -- I think three people have  
25 mentioned this -- should include a vehicle -- I mean,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 a control which is treated with the gold standard as  
2 saline and moist dressings versus the vehicle, versus  
3 the vehicle plus active drug? I mean, that's the only  
4 way you could clarify this question.

5 CHAIRMAN MCGUIRE: Clint.

6 DOCTOR CLINTON MILLER: That's essentially  
7 true. If there's a potential for the vehicle to have  
8 an effect, then you have to have its control is what  
9 you're fundamentally saying. And the way you do that  
10 is through a factorial design.

11 DOCTOR LIPSKY: The vehicle can have a  
12 negative effect as well, as at least one study in  
13 general in herpes where it looked as if the active  
14 product mixed in the vehicle worked, and in fact all  
15 it did was to counteract the negative effect of the  
16 vehicle, which is an inclusive dressing on the general  
17 herpes. So I think you can have an effect in either  
18 direction.

19 DOCTOR CLINTON MILLER: Right, absolutely.

20 CHAIRMAN MCGUIRE: Yes, Dr. Weiss.

21 DOCTOR WEISS: I think a very clear  
22 message that somewhere during private development  
23 there should be exploration of the vehicle alone.  
24 Sort of another question would be, what would be the  
25 best way, for instance if you're really interested in

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the vehicle you don't really think for pre clinical 1  
2 experience that it's harmful or terribly helpful, you  
3 know, you might not necessarily want to do, in you r  
4 large pre clinical trial have an entire arm o f  
5 patients that all go on that because, as we hear d  
6 yesterday, it's difficult getting patients in thes e  
7 trials, or hard to do.

8 It would be acceptable earlier in you r  
9 phase one and two testing to d o a smaller trial, some  
10 of the pilot type trials that Dr. Lavin was talkin g  
11 about, to satisfy the question about the vehicle alone  
12 before you move on to your pivotal phase three typ e  
13 trials.

14 CHAIRMAN MCGUIRE: Yes, Dr. Mindel?

15 DOCTOR MINDEL: Unlike yesterday's drug,  
16 usually dose response is done to find out the correct  
17 dosage that's optimum. And th at would be a nice time  
18 to have the vehicle tested ver sus the different doses  
19 in the preliminary to the major study.

20 CHAIRMAN MCGUIRE: Dr. Lipsky and then Dr .  
21 Margolis.

22 DOCTOR LIPSKY: Once having found a  
23 vehicle that seems safe and effective and has n o  
24 positive or negative effects, like we heard wit h  
25 becaplermin yesterday, it seem s to me that that might

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 be an easier way for the spons ors to go, is to simply  
2 say we have a product that's already been tested and  
3 found in these types of wounds, if we were to d o  
4 another study of neuropathic diabetic foot infections ,  
5 that would be a good vehicle to start with and no t  
6 have to repeat it all.

7 CHAIRMAN MCGUIRE: Dr. Margolis?

8 DOCTOR MARGOLIS: But getting back to the  
9 design of that trial, I mean you're basicall y  
10 designing a trial where you hope there's no differenc e  
11 between the standard care and your vehicle, so tha t  
12 changes are however that study goes, it's not going t o  
13 be a small little pilot study, it's going to end u p  
14 being a fairly substantial study. And someon e  
15 somewhere along the line needs to determine what a  
16 clinically important difference is. I mean if th e  
17 vehicle is ten percent better or ten percent worse, i s  
18 that okay, or is it 20 percent or 30 percent.

19 So, although I agree wholeheartedly with  
20 Dr. Lipsky that hopefully we'll only have to do th e  
21 trial once and then use the sa me vehicle for multiple  
22 different products. I sort of disagree with th e  
23 notion that it's a small little pilot study.

24 CHAIRMAN MCGUIRE: Dr. Weiss -- yes, Dr.  
25 Thomas and then Dr. Bergfeld.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DOCTOR THOMAS: I just want to make th e  
2 comment that in large clinical trials when you'r e  
3 comparing standard care to an agent that you think is  
4 likely to be effective, there would have to be a good  
5 reason to think that the vehicle is affected. And I  
6 would much rather see that done in phase one, phas e  
7 two than clinical trials just because of the ethical  
8 problems. I would not want to offer a vehicle a s  
9 acceptable care unless I had good reason to believ e  
10 that it would work.

11 CHAIRMAN MCGUIRE: Dr. Bergfeld?

12 DOCTOR BERGFELD: Well, philos ophically I  
13 would hope that the vehicle would add complimentar y  
14 healing powers to the active ingredients, so hopefull y  
15 in the development of the vehicle the concept woul d  
16 not be a no effect vehicle, but a vehicle tha t  
17 enhances as well as the active drug.

18 CHAIRMAN MCGUIRE: Dr. Weiss, have w e  
19 answered your questions?

20 DOCTOR WEISS: I think enough. I mean I  
21 still have confusion about --

22 CHAIRMAN MCGUIRE: In other words no?

23 DOCTOR WEISS: -- well, just the confusio n  
24 I would have, I guess, in terms of trying to advis e  
25 sponsors on when would be the best time or the optima l

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 way to explore the vehicle and to give us enough  
2 information about the vehicle --

3 CHAIRMAN McGUIRE: What I'm hearing is the  
4 earlier the better.

5 DOCTOR WEISS: -- but by the same token,  
6 earlier may -- usually you don't do very large trials  
7 until later in development. And as Dr. Margolis said,  
8 you know, the power of the study to detect a  
9 difference is very different than some of the smaller  
10 phase two trials where you're trying to just estimate  
11 some kind of treatment effect.

12 CHAIRMAN McGUIRE: Phil?

13 DOCTOR LAVIN: Yes. One suggestion that  
14 I have is that it might be a good area for NIH to fund  
15 some, you know, studies of vehicles. You know, there  
16 is a lot of research interest in an area. What's the  
17 ideal kind of vehicle, especially since all the  
18 studies that are likely to be done, just based on the  
19 number of people in the room here, it would be nice to  
20 see NIH come up with some kind of a grant or contract  
21 to do that.

22 DOCTOR WEISS: Would there be some sort of  
23 compatibility issues? Some of the various products we  
24 have may not, one vehicle may not be one size fits  
25 all, one vehicle may not necessarily be appropriate.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Or are there enough general aspects of vehicles that  
2 those kinds of studies can be done and used?

3 CHAIRMAN MCGUIRE: Well, you know, Dr .  
4 Weiss, some of the things that are considered to b e  
5 vehicles have major therapeuti c effect. I mean there  
6 may be a neutral vehicle out here, but I'm not sur e  
7 what it is. Dermatologists use rather bland vehicle  
8 preparations therapeutically. So you have a  
9 therapeutic, the point is you often have a therapeuti c  
10 effect with the vehicle.

11 Where are we? Yes, Dr. Mustoe?

12 DOCTOR MUSTOE: Yes. I would just would  
13 like to underscore that the both the expense an d  
14 ethical considerations are huge, and I would hope that  
15 if another manufacturer comes in with a  
16 hydroxymethylcellulose formulation that's, you know ,  
17 very slightly different that perhaps in that situatio n  
18 you would accept a small trial initially that lacked  
19 power to simply rule out a glaring problem with th e  
20 formulation. But I do think to require ever y  
21 manufacturer to do a 250 patient trial of standar d  
22 versus vehicle is, I think you 're setting the bar too  
23 high, it's not practical.

24 CHAIRMAN MCGUIRE: I think we're abou t  
25 wound down. I think we can ha ve a one hour break for

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 lunch.

2 I'm sorry?

3 DOCTOR DRAKE: Joe, I want to compliment  
4 the FDA for having this panel. I think addressin g  
5 this issue prospectively. I mean I just think th e  
6 discussion this morning has clearly demonstrated how  
7 difficult it is to design good clinical studies. I  
8 think what you've done here is real important because  
9 you're trying to prospectively address the questions  
10 instead of retrospectively.

11 Now, because of that I have a specifi c  
12 question and it relates to the neutrophic ulcers and  
13 the notion of whether, I mean I heard Fred, Dr .  
14 Miller, saying that debridement doesn't really matter ,  
15 I mean it matters, but it's not such an issue as it i s  
16 with pressure ulcers. In other words, you shouldn't  
17 have to do it after the first debridement. It seems  
18 like continuing debridement is acceptable standard in  
19 neutrophic ulcers. But when we looked at the dat a  
20 yesterday from Dr. Steve when he showed that, yo u  
21 know, additional slide after h is formal presentation,  
22 it was very clear at least to me that continue d  
23 debridement in those type of ulcers clearly affected  
24 the efficacy results.

25 And so I want to know what the take home

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 message that you folks from the FDA got from thi s  
2 discussion on that issue, because I'm very confuse d  
3 about it?

4 CHAIRMAN MCGUIRE: Lou?

5 DOCTOR FRED MILLER: Joe, can I clarif y  
6 what I said. You know, again I think that the initia l  
7 debridement is the effective one, or should be th e  
8 effective one. And if you're using a topical agen t  
9 and then you debride, obviously you're going to effec t  
10 if you're debriding the wound.

11 I was talking more about debriding callou s  
12 that might form around the wound. But in the woun d  
13 itself after your initial debr idement there should be  
14 very little intervention of that. As I said ,  
15 occasionally you're going to get a bony shard o r  
16 something of that nature that's going to be pulle d  
17 out, but any type of aggressive debridement after tha t  
18 initial impact I think would be not part of it an d  
19 would certainly impact on the findings. Thanks.

20 DOCTOR DRAKE: Well, how would yo u  
21 recommend conducting a study then, would you recommen d  
22 that the debridement be noted, but clearly defin e  
23 exactly what you were debriding. And is it you r  
24 opinion that no matter what you do, the mor e  
25 debridement you do, it raises the efficacy level o f

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 whatever agent you may be studying?

2 DOCTOR FRED MILLER: I think that you  
3 certainly have to define what type of debridement  
4 you're doing. And if you are just trimming callous,  
5 that's very different than debriding the depth of the  
6 wound. If you're using a topical wound healer and  
7 you debride the base of the wound, that certainly is  
8 going to have an impact. On our day to day activities  
9 where we're packing with, you know, with saline gauze,  
10 you know, we'll pull out any residual debride that  
11 might be there, but again it's that primary  
12 debridement that's important, and it certainly would  
13 impact ever using a topical agent. You would have to  
14 clarify what you've done. Thanks.

15 DOCTOR HARKLESS: Well, one point on  
16 that regard as related to the callous. There were  
17 several studies by Bolton in Manchester, England  
18 looking at callous, and just debriding callous and  
19 walking them on the optical fetobarograph decrease  
20 pressure 17 percent. So it was like proved that  
21 obvious. You know, being a doctor for 20 years I know  
22 that trimming a callous would decrease pressure and  
23 patients feel better. But he proved that, so I think  
24 that clearly agrees with Dr. Miller that what happens  
25 is, if they do walk they still develop callous around

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the area, and I agree with him that in the fact that  
2 that's what's usually debrided.

3 CHAIRMAN MCGUIRE: Karen, did you have a  
4 question?

5 DOCTOR WEISS: No, no. I just wanted to  
6 just comment, and I think Dr. Lavin I think said i t  
7 very nicely earlier, that if t he debridement is going  
8 on during the trial on these n eurotrophic ulcers that  
9 you ought to look at that and use some type of tim e  
10 dependent co-variate analysis and, you know, determin e  
11 whether or not that impacts where there is a  
12 differential use of this in on e arm versus the other.  
13 I think that's an important thing to note.

14 CHAIRMAN MCGUIRE: Wilma, did you have a  
15 comment?

16 DOCTOR BERGFELD: I do. I'd l ike to take  
17 up the subject of debridement again and suggest that  
18 there could be built into the protocol ways of gradin g  
19 and judging the debridement no t only on the frequency  
20 of debridement, but what is done minimal, moderate ,  
21 aggressive and maybe specific to callous versus base  
22 of wound. And that could be built in and that could  
23 be judged by the investigator on each visit.

24 CHAIRMAN MCGUIRE: I have the feeling tha t  
25 the debridement that Dr. Miller was talking about is

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1       debridement to blood. Is that correct, or debridemen t  
2       of what --

3                   DOCTOR FRED MILLER: Debridement to blood .

4                   CHAIRMAN McGUIRE: To blood.

5                   DOCTOR FRED MILLER: Initially.

6                   CHAIRMAN McGUIRE: In the photographs you r  
7       initial debridement --

8                   DOCTOR FRED MILLER: They frequently d o  
9       bleed, yes.

10                  CHAIRMAN McGUIRE: Yes.

11                  DOCTOR FRED MILLER: In fact they ver y  
12       often bleed, but the subsequen t debridement would be,  
13       you know, in the study would be the callous.

14                  And as Larry said, you know, if you'r e  
15       getting callous buildup, that indicates pressure o r  
16       friction, and that is going to also impact on th e  
17       healing of the wound which is in the center, or i t  
18       could certainly impact on the healing of the wound.

19                  DOCTOR WEISS: I just think this speaks t o  
20       me to having properly designed case report forms t o  
21       capture that information as the trial goes on, so the y  
22       can go back and retrieve that information in terms of  
23       not only the numbers, but the descriptive, you know,  
24       the various aspects about the debridement.

25                  DOCTOR LIPSKY: I think they have to b e

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 very objective. I think the concept of mild ,  
2 aggressive, surgeon's aggressive debridement might be  
3 quite different from a timid internist like myself .  
4 But we could define removal of all callous, removal of  
5 all necrotic material.

6 DOCTOR HARKLESS: Generally in a  
7 debridement you can have a pre ulcerative lesion and  
8 generally there is hemorrhage inter-callous prior to  
9 it actually breaking the skin. If they continue to  
10 talk on it, then it will actually become an ulcer.

11 So I think I agree with Dr. Miller, you  
12 have to debride it down to bleeding, and clinically  
13 that tells you whether there is actually blood there  
14 to form the fibrin plas for granulation tissue.

15 CHAIRMAN McGUIRE: Okay. Let's have lunch  
16 for an hour, and we will begin talking about entry  
17 criteria at 1:00 p.m.

18 (Whereupon, at 12:06 p.m., the meeting was  
19 adjourned to reconvene this same day at 1:13 p.m.)  
20  
21  
22  
23  
24  
25

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:13 p.m.)

CHAIRMAN MCGUIRE: All right, I think all of the committee that's in the room is seated. We are ready to start. There is a change in the afternoon schedule. We're going directly to topic five, which is endpoints. Topic five is -- Tracy asked me when we were going to have the open public hearing and we have two presenters who will speak after we discuss endpoints.

Under endpoints, which is topic five in your handout there are five separate issues, and none of the issues is particularly simple, so let's try to work through them.

"The Agency recommends wound closure as a primary efficacy endpoint for clinical trials of wound healing agents and devices. Some products currently under development and some not yet thought of, that's safe, may provide clinical benefit not measured by wound closure. Such wound care products are intended as adjuncts to healing or to provide wound care, for example control of wound odor or pain. Other products could fit under either indication, wound healing or wound care depending upon the claims put forward by the sponsors. Examples might include debriding agents

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 or antimicrobial agents.

2 Item one, ulcer closure. One propose d  
3 definition of ulcer closure is complete 100 percen t  
4 reempithelialization with no drainage or need fo r  
5 dressing. How should ulcer closure be defined an d  
6 measured?

7 Would anyone like to define it other than  
8 the words that the Agency has used "100 percen t  
9 reepithelialization with no drainage or need fo r  
10 dressing?"

11 Dr. Bergfeld?

12 DOCTOR BERGFELD: That's a timeles s  
13 question. Does that question mean at the time o f  
14 observation or does that include a follow-up period?  
15 I would recommend a follow-up period to make tha t  
16 conclusion.

17 CHAIRMAN MCGUIRE: Well, we're going t o  
18 talk about durability a bit later. We're talkin g  
19 about an endpoint. Now, you might ask how long do yo u  
20 have to have closure before you define it as a n  
21 endpoint, does it have to be more than ten minutes ?  
22 Probably. Should it be a month? Probably not. I  
23 mean I think we do need to put some limits on that ,  
24 and the Agency can work with t hat. Is that okay with  
25 you?

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Yes, sir?

2 DOCTOR MUSTOE: I was just going to say  
3 that I think I would omit the "need for dressing "  
4 because that is so subjective. Many people, or many  
5 patients will want to protect the area for a month ,  
6 two months, three months. I just don't see how that  
7 can be objectively defined.

8 CHAIRMAN McGUIRE: That's a very good  
9 point, especially with the stasis ulcers. The  
10 patients use protected dressings on them for a long  
11 time. That's a good point. Then you have the issue,  
12 does a compression stocking comprise a dressing ,  
13 etcetera, etcetera, it's a good point.

14 "Item two, for products defined" --

15 MR. CLINTON MILLER: May I make a n  
16 observation, sir?

17 CHAIRMAN McGUIRE: This is Dr. Miller.

18 MR. CLINTON MILLER: I call the definitio n  
19 as modified to me defines closed, not closure. An d  
20 that's two different things. There is a process o f  
21 closure, but there is a endpoint of closed .

22 CHAIRMAN McGUIRE: Okay, I think you r  
23 point is taken.

24 Is there clearer on the Agency side?

25 Yes?

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DOCTOR WITTEN: I would appreciate hearin g  
2 any comments on how well the panel thinks that thi s  
3 endpoint could be assessed, le t's say, by photographs  
4 and by two separate observers for example.

5 CHAIRMAN McGUIRE: Okay. We're gettin g  
6 into actually something rather complex. It i s  
7 possible for a wound to form a fibrin coat that looks  
8 very much like epithelia. And I don't know if we hav e  
9 reagents to diagnose that other than a biopsy. I' m  
10 speaking now, not from anyone else's experience, but  
11 from my personal experience in which I assumed that a  
12 wound had been epithelialized because it looked like  
13 it had. It was dry, glossy, but it really was no t  
14 epidermis. So the question is, do we have reagents t o  
15 identify reepithelialization.

16 Tom, that's probably something that yo u  
17 think about.

18 DOCTOR MUSTOE: I wish, I don' t know that  
19 there are any except histologically, but I can tel l  
20 you from animal studies, even doing very high powe r  
21 photographs of 20 power that the problem is there is  
22 a very thin epithelia before i t's heavily keratinized  
23 is fairly translucent, and so I just don't think thir d  
24 party -- I don't think blinded photography is going t o  
25 give you the precise endpoint. If you follow it over

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 two to three months, certainly at some point you can  
2 say yes this wound is closed, but I agree that t o  
3 define it, which is maybe very important in your study  
4 to say one is a month earlier than another, I just --  
5 photography is imperfect.

6 CHAIRMAN MCGUIRE: Well, not only i s  
7 photography imperfect, my pers onal observation of the  
8 wound is imperfect. And I'm glad you brought it u p  
9 because it's an item that I try to forget and it come s  
10 up periodically. And I think you might put that i n  
11 the category of things where we need extra help.

12 DOCTOR WITTEN: I'm sorry, things where we  
13 need?

14 CHAIRMAN MCGUIRE: We need, we need some  
15 other way to assess reepitheli alization other than --  
16 we need a non invasive technique to evaluat e  
17 reepithelialization.

18 Dr. Mustoe?

19 DOCTOR MUSTOE: I was just going to say,  
20 Dr. McGuire, and I don't know if you'd agree wit h  
21 this, but I would say that absence of drainage on a  
22 dressing for a defined two, th ree, four day period of  
23 time to me would qualify probably as epithelialized.  
24 It can't be just, as you say, a fibrin or an eschar,  
25 you can have no drainage for a small period of time.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 But if it's a long enough period of time, if it's  
2 opened, it will drain.

3 CHAIRMAN MCGUIRE: Well, I don't know what  
4 that period of time is. I can only tell you that I  
5 have seen wounds, chronic ulcerations, in genetically  
6 driven blistering disease and also in stasis  
7 ulceration where I thought clinically that healing had  
8 taken place, that the wound was closed and it was a  
9 dry wound or it was a dry surface. And so I have  
10 been, I am revealing to you that I have been tricked  
11 by the clinical observation. And I personally think  
12 that this is such a large issue that it would be good  
13 if we had a non invasive way of evaluation. But I  
14 think in general what you said, I agree with.

15 Yes, Dr. Margolis?

16 DOCTOR MARGOLIS: This is a clinical  
17 definition and you're asking clinicians to take a look  
18 and there is a published inter-rater reliability study  
19 looking at a fairly similar definition and whether or  
20 not multiple investigators could look at photographs  
21 and say whether or not the same wound was open or  
22 closed. The kappa was, I think, .68 or .69, so there's  
23 fairly good agreement. It's in lumenpare n  
24 regeneration from a couple of years ago, or actually  
25 from one year ago.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 CHAIRMAN MCGUIRE: Dr. Eaglstein?

2 DOCTOR EAGLSTEIN: Eaglstein from Miami.

3 I agree with you that this is really a problem are a  
4 where there's an unmet need. I would say recentl y  
5 there was a published study in Lancet using hydrogen  
6 prioxide placed on a wound and if it bubbled it wasn' t  
7 healed , and if it didn't bubble it was, and that' s  
8 misleading. We've looked at it very closely and I  
9 think what they should have said is if there is a  
10 crust there, it will bubble and it's still not healed .

11 But that aside, I just wanted to get that  
12 on the record, that that's an endpoint that go t  
13 published and there was no reference for it. I calle d  
14 the investigators and they promised me send me one and  
15 haven't. But that aside there , I think there isn't a  
16 way, a non invasive way to be sure you're go t  
17 epithelia. We published this so-called wrinkle test  
18 which, where you can press on an epithelialium and it  
19 will tend to wrinkle, which requires quite a bit o f  
20 training and it's very subjective still.

21 I think what Dr. Mustoe said is ver y  
22 important, photographs can throw you off because the  
23 thing epithelialium you photograph right through it.  
24 And of course if there is crust, you can't tell what' s  
25 going on below that.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 I think this issue really gets even more  
2 difficult when you reach a point that you're coming t o  
3 later with the tissue engineered or bioengineere d  
4 skins, because some of them take whether it' s  
5 permanent or for a period of time during which the y  
6 may be silently replaced. But there is a time whe n  
7 many of them are fully epithelialized and not weeping .  
8 And I think the part to me of what's implied in this  
9 question is, is that wound healed. And I think th e  
10 committee might be asked -- that question is bein g  
11 asked of the committee and I think a large number of  
12 those patients go ahead to be healed sometimes wit h  
13 that piece of tissue that appeared to take an d  
14 sometimes with a combination of that tissue whic h  
15 appeared to take and in the host tissue which seems t o  
16 invade the bioengineered tissue. And it's a very hard  
17 call.

18 CHAIRMAN MCGUIRE: Bill, I'm glad that yo u  
19 had as much trouble as I do with it, and thanks fo r  
20 supporting me in public. And it's clear to everyone  
21 that neither Dr. Eaglstein nor McGuire reviewed that  
22 manuscript on the peroxide.

23 DOCTOR EAGLSTEIN: And also I wanted t o  
24 mention on the third party observer that in genera l  
25 it's hard for even experienced investigators to alway s

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 make the right call. So then you have to find another  
2 person and try to train them to the same point where  
3 they can barely make the call. And so it does, it's  
4 not insurmountable, but finding that third person is  
5 very difficult. And when you come to the tissue  
6 engineered situation there is no way to blind until  
7 the healing has occurred because you'll always, even  
8 if you're the third person, you'll be able to see that  
9 there is some tissue in the center or covering most of  
10 the wound.

11 CHAIRMAN MCGUIRE: That's going to be  
12 another degree of complexity, but thank you.

13 Dr. Bergfeld?

14 DOCTOR BERGFELD: I just wanted to ask  
15 Bill Eaglstein a question, and that is to say in all  
16 of your experience with wound healing, those that are  
17 closed, is there a time period of monitoring just to  
18 see if they're actually healed? I mean is there a  
19 relative time period like six weeks, 12 weeks after  
20 the visual closure that one can assume it's closed if  
21 it maintains, I guess the word is durability, but I  
22 didn't want to apply it to this because I consider it  
23 part of the follow up of making the decision whether  
24 the wound has healed. Is there a window which one  
25 would apply to this for following to see if it

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 actually is healed?

2 DOCTOR EAGLSTEIN: You know, leaving the  
3 tissue engineered skins aside, in all the other cases  
4 I've always felt that remaining healed was primarily  
5 an issue of compliance. And I didn't think it wa s  
6 fair to blame the therapeutic agent if the healin g  
7 didn't last a long time.

8 You know, I think you could safely sa y  
9 well you could check for a week or two, but I thin k  
10 these ideas of months, several months or several more  
11 months are unreasonable unless you happen to find an  
12 agent which gives durable heal ing, more durable. But  
13 to blame the agent for the fact that it's not healed  
14 in a non compliant patient, it seems to me i s  
15 unreasonable. So I think if t here were any follow up  
16 along those lines, it would be within the week range.

17 Now on the bioengineered tissues I think  
18 it might require again a few weeks to be sure what's  
19 happening. So I think that a few weeks with standard  
20 therapy is being generous. A few weeks with tissu e  
21 engineered therapy is probably appropriate. Bu t  
22 months I think are unreasonable.

23 And also I think this whole idea o f  
24 durability overlooks many important things, becaus e  
25 there is a value in having a healed ulcer to people.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 There are even studies that show if you've healed your  
2 ulcer, like especially on a diabetic ulcer, you're  
3 more likely even if it recurs not to have as severe a  
4 problem or not to get the problem on the other foot.

5 And many times what you call a recurrence  
6 is a very small recurrence, which is quickly re-  
7 treatable. But in a study setting, which is reported  
8 to a review committee, it becomes recurrence even  
9 though it might be much, much smaller and easily dealt  
10 with. I hope you see what I'm saying. I think that  
11 talking about recurrences that way overlooks the value  
12 of having really healed the ulcer, even if it was only  
13 a one month heal. It changes the quality of life, it  
14 changes many things.

15 CHAIRMAN MCGUIRE: Thanks very much.

16 Dr. Stromberg, I overlooked you a minute  
17 ago, sorry?

18 DOCTOR STROMBERG: I'm with the FDA on the  
19 left there. Dr. Margolis is very modest. This is his  
20 paper which evaluated third party evaluation of  
21 photographs and whether they correlated with closure.

22 I want to ask him whether this was a  
23 series of photographs or a single time point  
24 photograph determining closure?

25 DOCTOR MARGOLIS: They were single time

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 point photographs of wounds that were either healed or  
2 within a week of being healed.

3 DOCTOR STROMBERG: Okay. I want to state  
4 my own experience in going through these clinical  
5 trials in which photographs were coupled with acetate  
6 tracings over time serial documentation of what the  
7 wound appeared, usually on a bi-weekly basis, at  
8 least. And I want to present before you my own view  
9 that, if evaluated over time, frequently photographs  
10 correlate with acetate tracing and give you a story of  
11 the wound's progress very reliably.

12 CHAIRMAN MCGUIRE: Thank you.

13 DOCTOR STROMBERG: I think this is  
14 particularly important in tissue engineered products,  
15 but you need to see them over time to determine  
16 whether you have a 100 percent reepithelialization and  
17 a bonafide closure or just a covering of the  
18 bioengineered product over the open wound.

19 CHAIRMAN MCGUIRE: But we're jumping ahead  
20 to the bioengineered products. But you agree that  
21 it's going to take a longer time to evaluate the  
22 durability of that process? And the nod was yes, I  
23 believe.

24 Is there more on ulcer closure?

25 The next item two, "For products defined

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 by the sponsor as wound healing agents," are there  
2 clinically meaningful endpoints other than complete  
3 closure? For example, what is the clinical  
4 significance of closure rate/partial closure? If  
5 partial closure, in the absence of healing, confers  
6 significant clinical benefit, how long must such  
7 partial closure be maintained to ensure that the  
8 benefit is realized? Should evidence of effect on  
9 partial closure in the absence of evidence of effect  
10 on complete ulcer healing be a basis for approval of  
11 a wound healing agent?

12 In other words, are we looking for  
13 products that produce partial closure? And I'm  
14 assuming that implied in this is partial stable  
15 closure, correct? Are there comments on this issue?

16 Yes, Dr. Thomas?

17 DOCTOR THOMAS: In terms of pressure  
18 ulcers, this gets to be a really complex thing, and I  
19 don't understand it all, but what happens in terms of  
20 partial closures, the way that a lot of studies are  
21 reported is that you take the beginning ulcer and the  
22 ulcer at the end of whenever your observation period  
23 is and call that difference, you know, the partial  
24 closure rate. And then if you divide that that by  
25 time, you get it right.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           The problem is that these wounds don' t  
2 heal linearly and so, you know, there is an assumptio n  
3 implicit in that sort of analysis that implies tha t  
4 there is a linear process, and it's non linear, it is  
5 parabolic. Wounds tend to accelerate to start wit h  
6 and then taper off and stay at a plateau, and then ma y  
7 go on up to healing.

8           There are several ways to handle that .  
9 One of the ways is to do an exponential analysis o f  
10 the wound closure rate, which is rarely done but has  
11 a lot of mathematical attraction about it. Th e  
12 problem with doing that is that it can never go t o  
13 zero because you reach infinity and so that's, yo u  
14 never can get it to complete healing if you use a n  
15 exponential rate .

16           I don't think it's really clear what the  
17 best way to measure partial healing rates are, whethe r  
18 you do this linearly or by per cent or by some sort of  
19 exponential progression, and because of that, thos e  
20 variables don't mean a lot to me. I think that yo u  
21 may have a wound that reaches a plateau and stays at  
22 that level for two to six weeks. In that situation i f  
23 the wound is not progressing, then clinically what we  
24 would do is try to change ther apy and see if we could  
25 get the wound to go back and accelerate toward

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 healing.

2 But unless you're seeing progression and  
3 you reach some sort of stable plateau, the best thing  
4 to do would be to simply continue the treatment and to  
5 see if you're just in a plateau at some ill-defined  
6 time.

7 But to answer the question in a summary is  
8 that I don't think that we have meaningful use for  
9 partial healing rates. I think we have to follow  
10 wounds to complete healing.

11 CHAIRMAN MCGUIRE: Do you mean because the  
12 analysis is complex?

13 DOCTOR THOMAS: Because the analysis is  
14 complex and I don't know what a 45 percent means. I  
15 don't know. That's an assumption that's linear. If  
16 we're going to make a 45 percent and we're going to do  
17 it by an exponential analysis, then I think that means  
18 something different. But we're making some linear  
19 assumptions that, if it's 45 percent at ten weeks,  
20 then it will be 100 percent at 20 weeks, but we just  
21 didn't follow the patients out to 20 weeks. That sort  
22 of assumption is built into that, and I think that  
23 that introduces some bias.

24 CHAIRMAN MCGUIRE: But what if it was 50  
25 percent at five weeks and it was the same 50 percent

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 at ten weeks and the same 50 percent at 15 weeks, is  
2 that of clinical merit?

3 DOCTOR THOMAS: Yes, that's non healing.

4 CHAIRMAN McGUIRE: Okay.

5 DOCTOR THOMAS: That means tha t it didn't  
6 work.

7 CHAIRMAN McGUIRE: But it started wit h  
8 zero, it stated with 100 percent wound, and you went  
9 to 50 percent of that area. Is there any benefi t  
10 there?

11 DOCTOR THOMAS: Well, I think if you coul d  
12 show that you had an experimental agent tha t  
13 consistently produced 50 percent wound closure an d  
14 stopped, then that would perhaps be of some clinical  
15 benefit. But if I were given the choice between that  
16 agent and an agent that went to 100 percent, I would  
17 choose the 100 percent.

18 CHAIRMAN McGUIRE: I guessed that.

19 Dr. Mustoe?

20 DOCTOR MUSTOE: Yes, I do think that Dr.  
21 Thomas' point is excellent, but I think that th e  
22 pressure source or perhaps in my experience the most  
23 non linear in their closure, but the most linear ,  
24 although they're not linear as well, but the mos t  
25 linear are venus ulcers. I guess I still think that

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 where I think that you're wound closure rate can be  
2 particularly useful is perhaps in a phase one or phase  
3 two study, but that the pivotal study still seems to  
4 me should be a complete wound closure. But I do think  
5 that there is value in a closure rate that can be ,  
6 that at least hopefully can be somewhat predictive.

7 And the reason I say that is I think it's  
8 very difficult in chronic wounds to get a significant  
9 power for complete closure unless you start off with  
10 a 400 or 500 patient study. And I don't think that's  
11 reasonable for a phase two study. And so I think you  
12 have to have an intermediate time point to have  
13 something meaningful.

14 MR. CLINTON MILLER: Client Miller. I  
15 tend to disagree with Dr. Thomas. I feel like that at  
16 a minimum the FDA should accept and promulgate the  
17 idea that this is a multi-dimensional problem. The  
18 design space is multi-dimensional, the treatment space  
19 is multi-dimensional, and the outcome space is also  
20 multi-dimensional. Those dimensions should include  
21 percentages that closed, it should include measures of  
22 reoccurrence, it should include the size of the  
23 reoccurrences, it should include partial closure. And  
24 I believe that you're going to need partial closure  
25 endpoints if you're going to have models and

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 statistical designs that are making observations over  
2 time.

3 You need to see the progress and the  
4 rates. I think that time is with us. Where we are  
5 seeing the effects of HCFA and other groups that are  
6 saying you can treat under the egregious of our  
7 support a particular wound for a particular length of  
8 time, yet it's 75 percent healed and suddenly you can  
9 no longer support the treatment program. So they back  
10 off and they start all over again.

11 I think that we need to keep track of that  
12 partial closure, and I think the problem in non linear  
13 closure is simply the fact that we as observers and  
14 designers and analysts have simply picked the wrong  
15 dimensions. That is, we should have picked something  
16 that was a log of whatever it was that we were looking  
17 at. And when you change those dimensions, the issues  
18 of non linearity and the closure disappear. So I'm  
19 thinking that because we picked a particular reference  
20 space, we can change that space and a lot of those  
21 problems would vanish.

22 CHAIRMAN MCGUIRE: Okay.

23 Dr. Cooper has a comment and then we'll go  
24 to the floor microphone.

25 Dr. Cooper?

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DOCTOR COOPER: I just would support 100  
2 percent closure and not partial closure because I  
3 think in the hands of good clinical sites that you can  
4 get up to 50 percent closure sometimes with just  
5 having been a participant in this study and having  
6 good standardized care that is consistently given, and  
7 I would not -- I mean I certainly agree that you need  
8 serial, you need some acknowledge of the serial  
9 changes in the wound, but I think that what we would  
10 all like to see is that wounds became healed.

11 CHAIRMAN MCGUIRE: Okay.

12 Floor microphone?

13 MR. ALVAREZ: Oscar Alvarez, New  
14 Brunswick. I've been doing wound healing  
15 research both clinically and at the pre-clinical level  
16 and I can tell you that there is an awful lot of  
17 advantage to having a product that increases the  
18 development of granulation tissue, although you never  
19 reach closure simply because of the fact, especially  
20 with drawn out clinical trials that can take months  
21 and months, if not years, for these wounds to  
22 completely heal. If you can granulate these wounds  
23 with an agent, you can then graft them, or perhaps  
24 reduce infection or reduce the risk thereof. I do  
25 think there is a tremendous value for a product that

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 enhances wound healing without complete healing.

2 CHAIRMAN MCGUIRE: Okay, thank you fo r  
3 your comment.

4 Yes, Dr. Drake?

5 DOCTOR DRAKE: I just want to support wha t  
6 the speaker just said. I think 100 percent standard  
7 on anything is unreasonable. I don't care whethe r  
8 we're dealing with psoriasis or onychomycosis or woun d  
9 healing. I think there's things that incrementall y  
10 get you where you want to go and that may be o f  
11 decided value to the patient. And for us to rul e  
12 something out that perhaps set the wound up so tha t  
13 you can close it or so you can do something to heal i t  
14 and so no just because it makes it better, we're not  
15 going to allow it to be in the mix is unreasonable.

16 I mean if there is something that cut s  
17 down on the bacterial content, if there is something  
18 that debrides, an agent that d ebrides a wound, it may  
19 not cause 100 percent closure, but in fact it ma y  
20 allow then the doctor taking care the wound to i n  
21 effect us a second modality th en to close it and have  
22 a better success rate. So I hate to see us lin k  
23 ourselves to 100 percent anything because I don' t  
24 think that's a reasonable standard.

25 CHAIRMAN MCGUIRE: Okay, that's clearl y

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 stated. And many of us have spent a lot of time  
2 preparing wound beds for grafts and for bioengineered  
3 products and I think there is validity in what you  
4 say. On the other hand, if you had your choice, your  
5 first choice, you'd just have the wound heal 100  
6 percent. That's not realistic probably.

7 Other comments?

8 Yes, Phil?

9 DOCTOR LAVIN: Yes, Phil Lavin. Two other  
10 endpoints. Obviously the compliment of complete  
11 closure time to complete closure and also something  
12 that might have helped the people yesterday which was  
13 this probability of being closed because any kind of  
14 product for example that increases the time to healing  
15 and shortens that as well as maintaining a comparable  
16 or superior, you know, healing rate, that would show  
17 very nicely in a graph of the probability of being  
18 healed as a function of time. So those are two other  
19 measures that I'd suggest in addition to proportion  
20 with complete healing.

21 CHAIRMAN MCGUIRE: Dr. Margolis?

22 DOCTOR MARGOLIS: What I was going to say  
23 is there is probably at least a half dozen papers now  
24 looking at wound closure rates and showing fairly  
25 similar rates among different types of chronic wounds

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 for wounds that ultimately go into heal. So there is  
2 literature to support the notion of a wound healin g  
3 rate. I'd also though argue on the other side as wel l  
4 though that if what you ultimately want from you r  
5 agent is that the wound is closed, then that's what i t  
6 should do. Whether it does it in a treatment pla n  
7 because you get good granulation, now you can ski n  
8 graft it closed, or if it does it because it does it  
9 all by itself, doesn't make a whole lot of difference  
10 to me.

11 But I guess, if I was evaluati ng an agent  
12 that I felt was going to allow things to take a skin  
13 graft sooner, just allowed for better granulatio n  
14 tissue that was bacteria free, then the way that I  
15 would want to see it approved would be in the context  
16 of a treatment plan of skin grafting or somethin g  
17 else.

18 CHAIRMAN McGUIRE: I think that you an d  
19 Dr. Drake were saying, that you should identify th e  
20 aims of the project at the beginning, and there ar e  
21 clearly different goals.

22 Other comment?

23 Yes, Dr. Thomas?

24 DOCTOR THOMAS: Just one additiona l  
25 comment to follow up on that. And I guess the reason

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 that I have strong feelings ab out 100 percent is that  
2 a lot of times when we are looking at studies, th e  
3 study duration is short, and when we're dealing with  
4 chronic wounds we're basically are looking at th e  
5 probability of a stage four healing inside of a year  
6 at 17 percent, you know, in general. So what you hav e  
7 to do then is make some substituted judgement and say ,  
8 okay, we can't take the trial that long and so we, yo u  
9 know, cut it off at some point and then we analyze th e  
10 rate in order to make that a secondary endpoint o r  
11 make it the primary endpoint and fully secondary.

12 I would just believe that, if we're going  
13 to look at chronic wounds, we need to do durations of  
14 studies long enough to be able to give us some goo d  
15 clear indications of what's going on.

16 CHAIRMAN McGUIRE: A response, David ?  
17 Let's have Margolis and then --

18 DOCTOR MARGOLIS: I agree wholeheartedly  
19 with what Dr. Thomas just said. It's a criticall y  
20 important point which I don't think was correctl y  
21 considered earlier when people were talking about --  
22 historical controls. As has been mentioned at least  
23 a half a dozen times now, if not more, wounds hea l  
24 over time, so if you're looking at 20 weeks you ma y  
25 find that only 40 percent of your wounds heal. If yo u

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 compare that to articles in the literature that say 80  
2 percent of venous leg ulcers heal, but they're using  
3 12 months, or 90 percent of diabetic leg ulcers, foot  
4 ulcers heal and they're using 14 months, those are  
5 very different comparisons and people need to be very  
6 careful with the duration of the study and what  
7 they're looking at.

8 And a lot of that is also confounded by  
9 the initial size of the wound and duration of the  
10 wounds, and some other risk factors, and for various  
11 people fairly well established as being important.

12 CHAIRMAN MCGUIRE: Dr. Rosenberg?

13 DOCTOR ROSENBERG: Yes. Sam Schuster  
14 wrote a piece once in The Lancet in which he said that  
15 the reason that dermatology was the most backward of  
16 the specialties was because it was the only branch of  
17 medicine in which the correct diagnosis was whatever  
18 the oldest dermatologist in the room said it was. I  
19 will take advantage of that position here to say that  
20 for any of you who, you know, wonder why this is  
21 dragging on so long, that those of us who have been in  
22 this for a time, the bones and junk and debris of  
23 former treatments for things that were supposed to  
24 help ulcers are beyond belief and very serious. And  
25 very bright people over time have suggested this

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 treatment or that treatment or the other treatment for  
2 skin ulcers, and they just are here today and none of  
3 them really, or very few of them --

4 CHAIRMAN MCGUIRE: I thought you were  
5 going --

6 DOCTOR ROSENBERG: -- so that any amount  
7 of time spent in doing what we're doing today is very  
8 well worthwhile in terms of helping the Agency to  
9 really come to grips with this. It's something that  
10 really needs to be done.

11 CHAIRMAN MCGUIRE: I thought for a minute  
12 you were going to say gold leaf or granulated sugar.

13 DOCTOR ROSENBERG: I remember the gold  
14 leaf, I've done gold leaf.

15 CHAIRMAN MCGUIRE: Okay.

16 Dr. Miller on my left?

17 MR. CLINTON MILLER: I just wanted to make  
18 an additional plea to the fact that this points out  
19 the importance of the assessment of treatment effects  
20 as a multi-dimensional problem because it's not just  
21 the total effect that closed, but it's also the rate  
22 at which we arrived at that closure. And what I would  
23 say is what we need is to recognize, we don't just ask  
24 the question "Is it effective?," but we also ask "Is  
25 it efficient?," has there been an efficient

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 utilization of resources to arrive at that endpoint.

2 So efficacy and effectiveness and efficiency al l

3 portray different dimensions t o those outcome issues.

4 CHAIRMAN McGUIRE: Karen, do you hav e  
5 enough on this point?

6 DOCTOR WEISS: I would say yes. I think  
7 that we've got some good advice from you and I' m  
8 happy--

9 CHAIRMAN McGUIRE: Okay.

10 DOCTOR WEISS: -- I'll ask dow n the table  
11 here whether or not my colleagues at Cedar or Ceda r  
12 Ridge have questions?

13 DOCTOR WILKIN: I thought it was helpful  
14 to hear that the committee seems to be allowing fo r  
15 two kinds of products, on whic h would be by itself it  
16 would have major activity, and another type of produc t  
17 which would be technique dependent. It would depend  
18 on other parameters of wound healing, perhaps get an  
19 ulcer to a specific stage and then grafting woul d  
20 occur. And I think that's very helpful because in th e  
21 very end it's not the Agency nor the committee tha t  
22 owns the drug product, it's the sponsor and th e  
23 sponsor needs to have that flexibility to determin e  
24 what it is they want to accomplish with their product ,  
25 and I think these guidance are very helpful for them

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 to think which way they want to develop --

2 CHAIRMAN McGUIRE: What I heard was that  
3 both goals are meritorious and they simply have to be  
4 identified.

5 Let's go on to ulcer recurrence. There i s  
6 a lot of information in this f irst sentence. I'm not  
7 sure I understand it all. "The quality of ulce r  
8 closure may vary depending, in part, on the effects o f  
9 wound healing products used. If an ulcer heals, it i s  
10 difficult to assess the quality of healing and th e  
11 clinical benefit." That's a statement. Question ,  
12 "How long should subjects be followed to asses s  
13 durability and cosmoses of ulcer healing?"

14 Okay, actually I'm having a little troubl e  
15 with the first and the second sentence. I don't have  
16 any problem with the question. But we can spend some  
17 time discussing either the statements or the question .

18 DOCTOR MARZELLA: Just as a clarification ,  
19 I think what was being asked i s making a distinction,  
20 for example, between a product that may just provide  
21 cover to a product that might, in addition t o  
22 providing cover, provide other functional aspects of  
23 what the skin normally does. So --

24 CHAIRMAN McGUIRE: You mean a  
25 bioengineered?

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DOCTOR MARZELLA: -- for example, yo u  
2 know, just a product that would provide just epitheli a  
3 cover for instance without, you know, the provisio n  
4 for sufficient dermis --

5 CHAIRMAN McGUIRE: Without a derma l  
6 equivalent?

7 DOCTOR MARZELLA: -- so this i s asking --

8 CHAIRMAN McGUIRE: So you're referrin g  
9 here primarily to grafts and bioengineered --

10 DOCTOR MARZELLA: Yes.

11 CHAIRMAN McGUIRE: -- okay.

12 Let's have some discussion. Yes, Dr .  
13 Cooper?

14 DOCTOR COOPER: I will say that some o f  
15 our follow up ranges between three months and on e  
16 year. And increasingly what we find is, of course ,  
17 the loner they have to be follow up the more we lose  
18 patients to follow up.

19 And also in many situations, p articularly  
20 with the older patient or with the person who is more  
21 dependent on social services, being able to get t o  
22 sites to be followed up is very difficult. S o  
23 although I do think that there should be some follow  
24 up in order to assess whether the wound has reall y  
25 stayed closed and perhaps the quality of healing ,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 etcetera, I think that that has to be increasingl y  
2 realistic as opposed to in the past when it could hav e  
3 been longer.

4 CHAIRMAN MCGUIRE: Dr. Cooper, what is the  
5 minimum time you would accept to indicate durability  
6 of closure?

7 DOCTOR COOPER: Well, it would reall y  
8 depend upon the wound. For a venous ulcer I think it  
9 would be longer, and for a pre ssure ulcer it would be  
10 longer. Usually if you've undertaken a diabetic stud y  
11 and you either taught them offloading or you've ha d  
12 orthotics made for them, what we find in our clini c  
13 because of the VA there is very good orthotics an d  
14 support for that. That they c ome to us and they stay  
15 closed , but they might have their shoes adjusted o r  
16 something like that.

17 Whereas the venous ulcer due to shearing  
18 and not really good laying down of any kind of a new  
19 basement membrane, they can have difficulty with that .  
20 So I guess I would say the venous ulcer three months  
21 and the pressure ulcer probably six months.

22 CHAIRMAN MCGUIRE: Okay. Well, that give s  
23 us something to work on.

24 Did you want to comment, Dr. Margolis?

25 Dr. Harkless, okay, whoever.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DOCTOR HARKLESS: In the neuropathic  
2 ulceration I look at one month. I call it the  
3 critical point, and generally within one month if you  
4 do not offload it effectively, it will recur. So I  
5 think that's very, very critical, if indeed it's  
6 epithelialized. And what happens in terms of the  
7 various interventions among specialists would depend  
8 on how often the patient is seen.

9 Medicare pays for routine foot care for  
10 two months, and so I think that particular patient  
11 would probably need to be seen every two months until  
12 they die.

13 CHAIRMAN MCGUIRE: Dr. Margolis?

14 DOCTOR MARGOLIS: With venous leg ulcers  
15 I guess I assume that what Dr. Cooper has mentioned is  
16 that patients are then wearing some sort of  
17 compressive garment permanently to keep the wound from  
18 recurring. If they don't do that, they can recur,  
19 they can rip their wound open as soon as their edema  
20 returns to their leg within hours or within days.

21 Certainly my feeling that, if the wound is  
22 healed for two to four weeks, then it's healed and  
23 anything after that is great. And the recurrence  
24 rates again for venous leg ulcers have been explained  
25 in a few studies. The best of which is a randomized

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 control trial looking at two different compressio n  
2 garments in patients who have healed, and it was out  
3 of England. And the recurrence rate is, I think ,  
4 somewhere between 30 and 50 percent per year dependin g  
5 on compliance with the compression garment.

6 That's not to say that the initial therap y  
7 didn't work, it's to say that it's recurrence fro m  
8 recidivism.

9 CHAIRMAN MCGUIRE: Dr. Rosenberg?

10 DOCTOR ROSENBERG: I spoke on thi s  
11 yesterday and this is not based on scholarly review,  
12 but just our own experience. We used to treat venous  
13 stases leg ulcers by having people admitted to th e  
14 hospital and putting them in b ed rest and doing pinch  
15 grafts, and they would heal and then they'd go out an d  
16 get them again. And now we treat them with th e  
17 compression bandage, the onaboat and beyond and n o  
18 tension to their skin, and the patients heal and they  
19 see that that's what heals it and most of them know t o  
20 keep on doing it by switching into proper support hos e  
21 or back into the onaboat or getting someone to be abl e  
22 to do it for them.

23 So there's a major difference in tha t  
24 instance in the recurrence rate. Not only do the y  
25 heal more easily, but they don 't recur, they don't --

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 we don't have the recidivism that we used to have when  
2 we treated the ulcers. We treat the leg and don't see  
3 recidivism.

4 CHAIRMAN MCGUIRE: Okay.

5 Yes, you had a comment or a question?

6 DOCTOR WITTEN: Actually just a question  
7 for the panel which is, I appreciate these comments  
8 about related to ulcer recurrence and how long the  
9 patient should be assessed. And the panel members  
10 have been using the term or commenting on how long  
11 they feel the patient should be followed after they  
12 heal, and I'm wondering how the use of that term was  
13 related to the definition of ulcer closure that you  
14 discussed in definition one. In other words, are you  
15 describing how long you think that the patients should  
16 be observed for recurrence, that they met the ulcer  
17 closure definition that we've described under part one  
18 of this question, or using the term "heal" in some  
19 other way to answer this question?

20 CHAIRMAN MCGUIRE: Well, I think you're  
21 hearing different degrees of durability for different  
22 clinical states. And I think Dr. Margolis suggested  
23 that a rather short period of time that the venous  
24 stasis ulcer is healed, then it's healed and if it  
25 breaks down later, it's because there was another

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 event. Is that what I'm hearing?

2 DOCTOR MARGOLIS: -- etiology -- I mean  
3 all these agents --

4 CHAIRMAN MCGUIRE: Mic.

5 DOCTOR MARGOLIS: I'm sorry. All these  
6 agents that we're considering are treating the wound,  
7 they're not treating the etiology, and they're not  
8 treating the insensitivity and the diabetic insensate  
9 wound, they're not treating the ambulatory venous  
10 hypertension and the venous wound, they're not  
11 treating the immobility from the pressure ulcer,  
12 they're all treating the wound. So the patient has a  
13 good chance of recurring because the etiology of the  
14 wound itself may or may not be successfully treated in  
15 the future. So you're asking the wound product to do  
16 something that it was never meant to do.

17 DOCTOR WITTEN: Actually I'm really just  
18 asking how your answer relates to the definition of  
19 ulcer closure that you all discussed under topic one,  
20 part one of this topic?

21 DOCTOR MARGOLIS: So I guess by that you  
22 would say that a wound is not closed unless it's  
23 closed for four weeks, is that what you're, since I  
24 said two to four weeks.

25 DOCTOR WITTEN: I'm saying when you talk

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 about that you should follow it, you suggest followin g  
2 it two to four weeks after it' s healed, I'm asking if  
3 when you use the term "healed," you mean the sam e  
4 thing as our definition of ulcer closure discusse d  
5 under topic one?

6 DOCTOR MARGOLIS: In a way, but no t  
7 completely. I guess you're asking for some sort o f  
8 durability and I'm saying it's closed for a few weeks ,  
9 I feel comfortable that it's really closed. My ow n  
10 definition for wound closure is a little bit differen t  
11 than yours and it's more in line with wound healin g  
12 society publication from a few years ago, which I  
13 think acceptably healed wound was a return to anatomi c  
14 structure and function, which sort of is encompassed  
15 in what you're saying.

16 And I feel, I guess what I'm saying with  
17 the two to four weeks is that's when I fee l  
18 comfortable letting the patient go out on their ow n  
19 saying you're healed and, you know, we'll see you les s  
20 frequently and let's be compliant with you r  
21 compression stocking.

22 I would still say they're healed when I  
23 think they're healed. I wouldn't delay it by a coupl e  
24 of weeks, if that's what your question is.

25 CHAIRMAN MCGUIRE: I don't particularl y

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 want to get into a semantic discussion between cured  
2 and closed. I feel you're implying something having  
3 to do with remodeling and greater durability than  
4 simple closure. And what I'm hearing is that four  
5 weeks, is that four weeks after a wound is closed,  
6 then that's history until the same pathological  
7 process causes the appearances of either a  
8 reappearance of that wound or another wound elsewhere?  
9 Is that a fair representation of what you're saying,  
10 Dr. Margolis?

11 DOCTOR MARGOLIS: Yes.

12 CHAIRMAN McGUIRE: Okay.

13 Dr. Rosenberg?

14 DOCTOR ROSENBERG: You know, I think  
15 that's why the HCFA has such a harder job than the FDA  
16 in terms of what they have to deal with. I mean Fred  
17 told us yesterday that having healed one of these  
18 neutrophic ulcers he's got a good shot at keeping it  
19 healed because he knows what caused it and he's worked  
20 with his patients and they stay well. And I've told  
21 you that our leg ulcers don't do as badly as they used  
22 to because the patients have been taught about walking  
23 and elevation and support.

24 And having found a pressure ulcer on a  
25 patient and healing it, how much luck do you have at

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 being able to change the situation so they don't get  
2 another one, what kind of a shot do you have at havin g  
3 patients not get another one?

4 DOCTOR ROSENBERG: Well, discouragingl y  
5 it's not very good. I think again, as it's pointed ou t  
6 this morning and there is a difference between a  
7 paraplegic and a quadriplegic and the elderly patient ,  
8 but we certainly do everything to try and teach th e  
9 family, try and get the suppor ted things that we can.  
10 But I mean there have been studies that have show n  
11 within a number of years that the ulcer has recurred.

12 I mean, you know, we don't know each othe r  
13 very well, but having heard you talk about your clini c  
14 and everything else, I'm quite sure that there is an  
15 educational piece, and everything else that peopl e  
16 take home with them. And, you know, that's just such  
17 a big piece of this which really doesn't intersect th e  
18 FDA, but it means everything in terms of how th e  
19 patients do.

20 CHAIRMAN MCGUIRE: Yes, Dr. Thomas, an d  
21 then whose up? Okay, Dr. Thomas and then I'll go ove r  
22 to you, Dr. Harkless.

23 DOCTOR THOMAS: I'll give you just som e  
24 data from our experience with pressure ulcers. I s  
25 when you look at a multi-varied analysis in terms of

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 risk factors for pressure ulcers, the one that I think  
2 came in second out of five is a history of a previous  
3 ulcer. Their recurrence rate in elderly people is  
4 very high, and part of the problem in terms of  
5 education is that the patients are not able to do  
6 anything to prevent the ulcer themselves, so they're  
7 relying on other people to do that, which doesn't  
8 always work.

9 But in terms of recurrence rates, at least  
10 in pressure ulcers, I'm sort of with David, I mean  
11 when it's healed it's healed. Then I'm going to try  
12 to do everything I can to keep it from coming back.  
13 The problem I'll get into is that that tissue is not  
14 normal, it does not have an anatomic restoration, and  
15 it's always going to be susceptible to more breakdown.  
16 And the problem that we actually run into is in  
17 getting patients offloaded from that pressure ulcer,  
18 we just create one on the other side.

19 DOCTOR ROSENBERG: Are there products that  
20 you can buy that FDA has ruled on as a device that  
21 prevent recurrences?

22 CHAIRMAN MCGUIRE: No.

23 DOCTOR ROSENBERG: Is there that industry  
24 -- are there products that you would prescribe the day  
25 that the patient is pronounced healed, that I want you

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 now to use this indefinitely and put it on ever y  
2 night , or wrap this around every afternoon, o r  
3 anything like that, are here such devices on th e  
4 market?

5 DOCTOR THOMAS: There are devices on the  
6 market and I would try and do that, but that's anothe r  
7 very complicated subject. It creates a tremendou s  
8 burden for the patients in that it's not paid for .  
9 Prevention or stage one or stage two are not, n o  
10 devices are paid for for that, and so normally whe n  
11 you get a bad ulcer is the only time you can use that .  
12 When it's healed, then they're at risk, but you get a  
13 great deal of difficulty prescribing some devic e  
14 that's going to prevent them from getting another one .

15 CHAIRMAN MCGUIRE: Dr. Harkless?

16 DOCTOR HARKLESS: Yes, I think th e  
17 parameter of occupation will play a role in th e  
18 durability because patients that stand while janitors ,  
19 civil engineer helpers that stand all day will have - -  
20 I would think. Dr. Margolis and I mentioned that, an d  
21 I think he agrees with me from a venous ulce r  
22 perspective too. Because to me the most difficul t  
23 thing I see as a podiatrist is trying to control edem a  
24 from a surgical perspective or whatever it may be is  
25 important.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           One point about the device, neuropathi c  
2 ulcer, Bolton did a study over in Manchester looking  
3 at socks, and he showed that socks decrease pressure  
4 27 percent. If you're familiar with the thoreal ,  
5 that's where he decided he wanted his company in the  
6 health business, not the sock business. There's a ne w  
7 company called Therasock that's a spinoff of that that  
8 also has socks. And then you have Siliphose has sock s  
9 with some silicone in them that's supposed to offload .  
10 I have not seen any published data in that regar d  
11 however.

12           CHAIRMAN MCGUIRE: Okay.

13           Karen?

14           DOCTOR WEISS: I guess the question o f  
15 this discussion, we heard in question one that there  
16 should be, to determine that something is healed o r  
17 closed, there should be a mini mum period of time that  
18 you assess that wound, but then the question wit h  
19 three with recurrence and the difficulties and th e  
20 fact that it involves some multi-factorial, shoul d  
21 trials even be designed to capture recurrence rates?

22           I mean it was done and we felt it wa s  
23 useful in the part that we discussed yesterda y  
24 primarily because we want to make sure that th e  
25 recurrence rates weren't worsened or increased, but i s

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 that something that should be built into trials given  
2 the fact that it's not really going to be so much an  
3 assessment of the actual part we're discussing, but  
4 all sorts of other patient management compliance  
5 issues. Is it something that we should even ask  
6 people to capture?

7 CHAIRMAN MCGUIRE: Well, the data can be  
8 captured. I think you have to be very careful how you  
9 use the data because if an individual has incompetent  
10 venous valves and is 55 years old and is working at  
11 two jobs, as I think all of my patients are, then once  
12 you heal that ulcer there is going to be inevitably I  
13 think a recurrence because her valves are not going to  
14 get better and, you know, she will be as compliant as  
15 she will be, but she's also taking care of her mother,  
16 and it's very complex.

17 I think faulting a product because there  
18 is a recurrence is a very chancey thing to do and you  
19 have to look at it very carefully. Because we haven't  
20 changed the basic pathology.

21 Dr. Eaglstein?

22 DOCTOR EAGLSTEIN: It seems to me that the  
23 committee shouldn't advise the Agency to look long  
24 term into this healing. That's what's being asked now  
25 I think rather regularly. And what you're really

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 saying is when you do a study of an agent that the  
2 sponsor says will heal wounds, then at the end of the  
3 study you have to show how capable you are of keeping  
4 people in compliance for whatever period of time the  
5 Agency says they want you to. I mean it's a totally  
6 different game, you've changed the game entirely.

7 CHAIRMAN MCGUIRE: That's correct.

8 DOCTOR EAGLSTEIN: And I don't see why we  
9 should buy into that notion. I think it has some  
10 value in the one sense, as you say you would like the  
11 healing to be at least as good, and it would be great  
12 if it was better, but the whole game is different, the  
13 agent is to heal the wound. And then you say well  
14 also you have to prove that you can ensure compliance  
15 for three months so it will stay healed, well that's  
16 a different game, that's a different set of challenges  
17 for the sponsor.

18 So I think that I would recommend the  
19 committee not advise these long follow up periods very  
20 much at all because you're just advising a different  
21 set of challenges.

22 CHAIRMAN MCGUIRE: Well, I can see some  
23 merit in capturing the data. I think you have to be  
24 very careful how you use the data because it is  
25 conceivable, it is conceivable that there will be a

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 product that is worse than all the others in terms of  
2 durability. And if that were the case, you'd have to  
3 look into it as an issue of more than compliance. But  
4 I agree compliance and lifestyle are the big issues.

5 Who is up? Dr. Lavin?

6 DOCTOR LAVIN: Yes, I think, you know, in  
7 picking up on that point and looking at duration of  
8 healing, I think that it's a good endpoint to look at.  
9 But keep in mind that if you only have a 40 percent  
10 healing rate, you're never going to have the  
11 statistical power to be able to discriminate between  
12 the difference in relapse rates between the two arms  
13 or three arms that are under study. So it's the kind  
14 of thing that's probably best in the phase four  
15 setting than it would be in the a phase three setting.

16 CHAIRMAN MCGUIRE: Yes, Tom?

17 DOCTOR THOMAS: Yes, I would just simply  
18 say, and I think that perhaps has been directed, that  
19 I think tissue engineered products, just to underscore  
20 what Dr. Eaglstein said, I think that before you can  
21 consider wound closed, I think a month is a minimum  
22 amount of time that you have to follow that to  
23 actually say that stable closure has been achieved.

24 CHAIRMAN MCGUIRE: Okay.

25 DOCTOR THOMAS: And I also think that a

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 three month follow up for all studies is a  
2 conservative period of time. If the recurrence rate  
3 is dramatically higher, I think that is an issue that  
4 would be relevant to the FDA, so I think a three month  
5 follow up for chronic wounds is a reasonable  
6 compromise.

7 CHAIRMAN MCGUIRE: Okay.

8 Dr. Marzella, I think you've heard it  
9 several times. I think you've heard the same thing  
10 several times.

11 I'm ready to go on. Do you have something  
12 else to say about durability, Dr. Drake?

13 DOCTOR DRAKE: Yes, I just, maybe three  
14 months is reasonable, but I think you're mixing apples  
15 and oranges because that's not the challenge put forth  
16 by a wound healing agent. Does it heal the wound, and  
17 the answer is yes or no. Or does it help heal the  
18 wound? Does it increase the rate of wound healing?  
19 I think those are the issues.

20 I guarantee you that I don't have the  
21 volume of patients that these guys do with wounds, but  
22 I'll promise you I have had many patients who have  
23 managed to get a wound closed and then three months  
24 later it's broken down because they went back to work  
25 and they started taking care of their children, and

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 it's not the least bit fault of the thing you wer e  
2 using to help heal the wound, and I think you'r e  
3 mixing apples ad oranges. So I would argue strongly  
4 against the follow up, long fo llow up, because that's  
5 not what you're measuring.

6 CHAIRMAN MCGUIRE: You've heard the follo w  
7 up both says. Let's go to item four. Item four, "Fo r  
8 products defined by the sponso r as wound care agents,  
9 what are clinically meaningful efficacy endpoints ?  
10 What should be considered adequate demonstration o f  
11 safety?" So we're talking abo ut efficacy and safety.  
12 "Please consider the following types of products :  
13 Wound debriding agents."

14 We've really not talked very much abou t  
15 the wound debriding agents over the last day or so .  
16 "Some would argue that if an agent debrides a woun d  
17 effectively, a meaningful clinical outcome is reached .  
18 Others argue that the ability of agents to remov e  
19 portions of necrotic tissue is not by itself a n  
20 adequate measure of clinical benefit and an agent with  
21 such an effect could nonetheless potentially impai r  
22 healing.

23 Because of these uncertainties, les s  
24 ambiguous measures of benefit should be demonstrated.  
25 If the sponsor of a debriding agent is not seeking an

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1       indication as a wound healing agent, other than  
2       improved wound closure, what beneficial effects should  
3       be demonstrated to clearly establish benefit?"

4               Okay, that's a very complicated statement  
5       and question, and I'm happy to hear from anyone on the  
6       panel.

7               Yes, Dr. Lipsky?

8               DOCTOR LIPSKY: I think the fact that you  
9       haven't heard anything about wound debriding agents  
10       speaks volumes.

11              CHAIRMAN MCGUIRE: I know why.

12              DOCTOR LIPSKY: Go ahead.

13              CHAIRMAN MCGUIRE: No, go ahead.

14              DOCTOR LIPSKY: I think the fact of the  
15       matter is that there is not much data that they're  
16       effective, and the only data I would be convinced by  
17       is a comparison of a wound debriding agent with  
18       mechanical debridement which we know to be effective.

19              And I think that there is danger in such  
20       an agent that it would be easier to use it rather than  
21       do the mechanical debridement, so I'd be very  
22       concerned unless there was studies that I'm unaware of  
23       that these mechanical debriding agents are equivalent  
24       to appropriate sharp debridement.

25              CHAIRMAN MCGUIRE: Okay. Now, there are

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 two issues here. One is whether the types o f  
2 chemical, types of chemicals and enzymatic debridemen t  
3 work and are effective. That' s one issue. The other  
4 is whether we are using them at the present time. An d  
5 then the other is how you would measure them, ho w  
6 would you measure their efficacy and safety if yo u  
7 wanted to, how would we advise the Agency.

8 Dr. Harkless?

9 DOCTOR HARKLESS: Clinically I used to no t  
10 use debriding agents at all. However, my limite d  
11 applications are in wounds that are left open afte r  
12 we've taken them to surgery. In that margina l  
13 diabetic foot where there are some patchy granulation  
14 tissue interspersed between some fibrous connectiv e  
15 tissue. And I agree that you need to steal the blade  
16 to do that, but I have seen improvement in certai n  
17 wounds where we will put a little Accuzyme or whateve r  
18 in there, whatever you choose to place in there, and  
19 that's due to the fact that we have a wound cente r  
20 where we have a hyperbaric cha mber and we have two or  
21 three nurses over the past two years that have bee n  
22 insistent on utilizing that in certain cases.

23 CHAIRMAN MCGUIRE: Now, wait. I think th e  
24 question is, if the Agency wanted to look at debridin g  
25 agents, how would we advise them to look at them .

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 It's not whether I'm using the m or you're using them,  
2 the question is how would we advise the Agency t o  
3 evaluate them for safety --

4 DOCTOR HARKLESS: Well, I will agree with  
5 Dr. Lipsky. I will agree with him that you can't ,  
6 there's no data.

7 CHAIRMAN McGUIRE: Yes.

8 Dr. Cooper?

9 DOCTOR COOPER: I don't use them, but if  
10 I was to advise the Agency, some of the criteria woul d  
11 be the time, the duration of t ime before the necrotic  
12 tissue or whatever was in the wound was removed, I  
13 think, and the ease of application. And I think the  
14 amount of other things that ha d to be used to utilize  
15 the product.

16 The reason I say that is if you were goin g  
17 to do studies in nursing homes of pressure ulce r  
18 patients where in some nursing homes even in studies,  
19 the ability to debride patients in the nursing home i s  
20 not as convenient as it is in hospitals. So if yo u  
21 were not allowed to hospitalize a patient and you wer e  
22 going to use a debriding agent as part of it, I think  
23 those would be some factors that I would consider.

24 CHAIRMAN McGUIRE: Dr. Mustoe?

25 DOCTOR MUSTOE: Yes, I think that th e

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 problem, this is a very very difficult problem o r  
2 question and probably one of the most difficult ones  
3 here. These products are used and people hav e  
4 clinical impressions, but I do think the Agency i n  
5 considering new products has a responsibility to make  
6 sure the product is not worse, does not in some wa y  
7 make the wound worse. And I guess here is wher e  
8 perhaps an intermediate wound closure time point woul d  
9 be useful.

10 I think if you're going to use a debridin g  
11 agent for a month, then you need to have a control ar m  
12 and show that your wounds are healing at the same rat e  
13 as, let's say, mechanical and surgical debridement .  
14 And I think that that is perhaps a doable study i n  
15 terms of expense. It doesn't -- I think to hold it t o  
16 the standard of complete wound closure is no t  
17 acceptable, or I mean it's jus t not practical. But I  
18 think if you don't have some objective wound closure  
19 rate as part of your measure, then you unfortunately  
20 are going to get some products on the market that are  
21 making wounds worse.

22 CHAIRMAN MCGUIRE: Dr. Lipsky?

23 DOCTOR LIPSKY: I'm having a hard tim e  
24 visualizing the study. We spoke earlier about th e  
25 fact that we think that debridement for most wounds i s

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 a one time event, if you do it right, and only in some  
2 instances might you need to pare back callous.

3 If we were to have a mechanical debriding  
4 agent, we'd have to be looking at I guess two issues,  
5 one is, can it be used without any mechanical  
6 debridement if we had an enzyme debriding agent?  
7 Could we put it on the wound and not have to use any  
8 mechanical debridement? That would be the first  
9 issue. And if we say well, no, it doesn't even get to  
10 where it needs to go if there's all this eschar and  
11 callous and so on, then the question would be after  
12 you've done scalpel debridement, does it have any  
13 benefit thereafter? And if what we've said is that if  
14 you do proper scalpel debridement, you don't need any  
15 further debridement, why would you need that agent?

16 CHAIRMAN MCGUIRE: Ken Hashimoto?

17 DOCTOR HASHIMOTO: In dermatology  
18 practice, and of course in the primary care situation,  
19 we just don't do debridement, and we just don't do  
20 scalpel operation like things. So the product --  
21 fiber -- type of agent definitely has place in actual  
22 practice and particularly in office practice.  
23 Effective agent available, it's very beneficial.

24 CHAIRMAN MCGUIRE: I would like for us to  
25 concentrate on design to design efficacy and side

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 effects dangers rather than our current clinica l  
2 practice because I suspect there is different clinica l  
3 practice all around the table.

4 Who was next? Dr. Mustoe?

5 DOCTOR MUSTOE: I'll just say one mor e  
6 thing. I think a simple design for instance for a  
7 debriding agent would be to compare surgica l  
8 debridement versus in a defined non surgica l  
9 debridement with your debriding agent and compar e  
10 wound closure rates over, let' s say, a defined period  
11 of time like six weeks, and if the debriding agent wa s  
12 as good as surgical debridement I think it' s  
13 worthwhile. I don't think you have to say it' s  
14 better, but on the other hand if it's much worse and  
15 the wounds are doing much more poorly, then it doesn' t  
16 have a place.

17 CHAIRMAN MCGUIRE: You're going to speak  
18 to debriding agents?

19 MS. BRYANT: Ruth Bryant. The comment I  
20 would make about debridements, there's many ways t o  
21 achieve debridement clinically, and I think a lot of  
22 factors contribute to which method you choose to use  
23 that have to be considered. And I think, if you'r e  
24 going to look at debriding, then debriding is th e  
25 issue. If you're looking at debriding agents, yo u

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 have to look at the outcome of why you're debriding,  
2 which is cleansing the wound. And I think how long  
3 does it take you to get rid of the necrotic tissue is  
4 what you have to measure.

5 The idea of healing is not going to even  
6 begin while you're removing the necrotic tissue, so to  
7 look at closure or healing status to me seems like  
8 you're again mixing apples and oranges.

9 So I guess I would look at some outcome  
10 measures like how long does it take to get the wound  
11 cleaned up. You can't really compare it to surgical  
12 debridement because obviously that's automatic, you're  
13 going to have to look at autolysis methods or sharp  
14 debridement methods. And I would think some outcomes  
15 are increased in the site and drainage and length of  
16 time that you'd look at, and maybe infection rates.

17 CHAIRMAN MCGUIRE: Yes, Dr. Thomas?

18 DOCTOR THOMAS: Just to echo what's being  
19 said in terms of debridement, there is a place for ,  
20 you know, these debriding agents or topical agents  
21 that do debridement. And when we were talking about  
22 debriding wounds before we put on another agent, I  
23 think that's a different issue . This would be wounds  
24 that hadn't been debrided, you could design that.

25 The problem that you're going to get into ,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 as she points out is, you're going to have multiple  
2 arms because if you've got a tremendous amount of  
3 necrotic material, you're going to want to use  
4 surgical debridement. If you have a small amount,  
5 then you may want to use one of these or you may want  
6 to use some autolytic method.

7 The real issue to me seems to be the issue  
8 that Tom brought up and that is, does this slow the  
9 wound down, is it harmful to use that, and that means  
10 you have to follow the wound with whatever it's  
11 treated with after debridement in order to get some  
12 idea of time to partial closure or time to complete  
13 healing.

14 CHAIRMAN MCGUIRE: I would see this as a  
15 two phase observation. One is when the eschar is  
16 gone, when that's gone. And then the second point is  
17 when it heals. Now, if one technique got rid of the  
18 material very quickly, but it never healed, it  
19 wouldn't be a very good deal. And so I really think  
20 we'd have to look at both points.

21 Dr. Eaglstein?

22 DOCTOR EAGLSTEIN: Actually I think you  
23 did address the policy issue, which I think there was  
24 a hearing on this last summer, which I hope concluded  
25 that these agents should do what they claim to do. I N

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 other words, it's to debride, it should debride. If  
2 it's to reduce the microbial load, it should reduce  
3 the microbial load. If it's to reduce pain it should  
4 reduce pain. The question to me is are these valuable  
5 endpoints?

6 I think in the practice of medicine many  
7 feel it is. We want the Agency to give us safe  
8 materials that do what they say they'll do. They  
9 don't say they'll heal wounds.

10 I think for a while the Agency had the  
11 idea that anything that went on a wound could only be  
12 measured by whether it heals a wound or not, but as  
13 clinicians I believe we know that some wounds will  
14 eventually heal or heal at a slower rate, but whether  
15 they heal or not we want to get rid of that eschar, we  
16 want to get rid of that debride, we want to reduce the  
17 pain, we want to reduce the microbes, and we want safe  
18 agents that do that. So I would urge the committee  
19 not to recommend adding in healing.

20 CHAIRMAN MCGUIRE: Bill, I don't think  
21 you've heard that. I think what you heard is that we  
22 would like for the sponsor to measure what the goal of  
23 the product is, whether it's debridement, whether it's  
24 analgesia, whether it's reducing the microbial load.

25 But then I can't, and this is a personal

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 view, I can't avoid wondering what's going to happen  
2 to that ulcer three months down the line. And i f  
3 there was a substantially, if there was a substantial  
4 decrease in healing, then I think that would b e  
5 pertinent. But I agree with you, I agree with you ,  
6 the first point that's the first target, have yo u  
7 reduced the microbial load, or have you reduced odor,  
8 have you reduced pain, have you reduced the debride.

9 Yes, Dr. Lipsky?

10 DOCTOR LIPSKY: One last point on this .  
11 The question is what beneficial effects should b e  
12 demonstrated. Other other parameter I think that' s  
13 worth looking at is pharmacoeconomics. It cost a  
14 certain amount of time on the physician, nurse ,  
15 whoever is doing the debridement initially, but i f  
16 that's the end of it, then that has to be compare d  
17 against a daily or several times a day applicatio n  
18 over a period of several days or longer. And I think  
19 the Agency ought to be looking at that question a s  
20 well.

21 CHAIRMAN McGUIRE: Dr. Rosenberg?

22 DOCTOR ROSENBERG: People say we ought to  
23 define terms here. We've been talking yesterday and  
24 up until now about ulcers. We've talked abou t  
25 diabetic ulcers and neurotrophic ulcers, and stasi s

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1       ulcers and pressure decubitus ulcers. Now, we'r e  
2       talking about wound and wound care. And wounds an d  
3       ulcers are two different things. I mean for wound s  
4       we're talking a little girl abrades her knee or th e  
5       patient whose had a laser acco mplished resurfacing of  
6       her face, neck and --

7                   CHAIRMAN McGUIRE: Bill, wait, wait, wait .  
8       I think we're still talking about ulcers.

9                   DOCTOR ROSENBERG: We're still on ulcers?

10                  CHAIRMAN McGUIRE: Yes, we're not talking  
11       about lacerations, abrasions, incision wounds --

12                  DOCTOR ROSENBERG: Well, we used to talk  
13       about wounds, I beg your pardon --

14                  CHAIRMAN McGUIRE: -- we're talking  
15       about --

16                  DOCTOR ROSENBERG: -- and maybe we ought  
17       to talk about ulcers and not wound care I think.

18                  CHAIRMAN McGUIRE: Okay, we're talkin g  
19       about necrotic ulcers, stasis ulcers, ischemi c  
20       ulcers.

21                  DOCTOR ROSENBERG: I thought we ha d  
22       changed, we're still on ulcers.

23                  CHAIRMAN McGUIRE: Yes, Karen?

24                  DOCTOR WEISS: You've almost addresse d  
25       really parts of the question four, A, B, C and D ,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 because you've been telling us that these product s  
2 should do primarily what they're intended to do. I  
3 guess my question with all of these though is tha t  
4 these are somewhat subjective type of endpoint. These  
5 would probably be open type of studies, and so I'm no t  
6 quite exactly sure what I'm asking, I'm mus t  
7 expressing my concerns that they may be very difficul t  
8 to determine some of these kinds of measures because  
9 of the nature of what they nee d to show and the kinds  
10 of trials.

11 CHAIRMAN MCGUIRE: I'm missing it. Bu t  
12 we're still in response to Dr. Rosenberg, we'r e  
13 talking about --

14 DOCTOR WEISS: We're talking about ulcers -  
15 -

16 CHAIRMAN MCGUIRE: -- we're talking  
17 about --

18 DOCTOR WEISS: -- classes of ulcers --

19 CHAIRMAN MCGUIRE: -- we're ta lking about  
20 ulcers --

21 DOCTOR WEISS: -- yes --

22 CHAIRMAN MCGUIRE: -- and we're talkin g  
23 about the effects --

24 DOCTOR WEISS: -- but question fou r  
25 addresses the different types of agents that you can

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 use on these various kinds of ulcers, the debridin g  
2 agents, topical analgesics, et cetera. And in general  
3 you've been saying that the fi rst thing is that these  
4 types of agent should do what they're intended to --

5 CHAIRMAN MCGUIRE: right.

6 DOCTOR WEISS: -- whether it's go debride ,  
7 to relieve pain --

8 CHAIRMAN MCGUIRE: Correct.

9 DOCTOR WEISS: -- and you're saying that  
10 as the first step, and there was a lot of discussion  
11 about whether or not once you look at some assessment  
12 of closure too, maybe as a safety issue, but certainl y  
13 that should be something that many people are saying  
14 that we should look at. And I appreciate thos e  
15 comments, but I guess my question will just be then,  
16 in terms of designing to look at these kinds o f  
17 endpoints, things like debridement, we'll take as an  
18 example, it seems to me that that is somewha t  
19 subjective. The endpoint of removing all necroti c  
20 tissue , is that something where one could just loo k  
21 very clearly and say it it is, or not it isn't? I t  
22 seems to me it's somewhat subj ective and that it's no  
23 going to be maybe all that clear cut. If you'r e  
24 trying to see whether or not something is better o r  
25 just as good as a debriding agent it's not necessaril y

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 going to be all that very easy to determine that.

2 CHAIRMAN MCGUIRE: Well, Karen, it i s  
3 subjective, and if I look into the depths of th e  
4 pressure ulcer and the residen ts looks into the depth  
5 of the pressure ulcer, we generally agree that there  
6 is necrotic material in or that's clean. And whe n  
7 it's clear we say that's wonderful, and the resident  
8 says that looks wonderful, you know. I mean it i s  
9 subjective, but one can tell the difference betwee n  
10 the clean base of an ulcer and debride in the ulcer.

11 I don't know, Dr. Thomas?

12 DOCTOR LAVIN: That's not quite the answe r  
13 I needed to hear.

14 CHAIRMAN MCGUIRE: Well, maybe it' s  
15 because I'm just making it too easy.

16 Dr. Thomas, tell us?

17 DOCTOR THOMAS: I think that's the whole  
18 point. And obviously the way to get around that i s  
19 to, you know, if you really want to know about it, yo u  
20 have two people look at it and see what the capiti s  
21 is, you can do that. You can't take photographs, the y  
22 are hard to use, but I do think that everyone of thes e  
23 things in terms of necrotic material, granulatio n  
24 tissue, epithelialization is all subjective to som e  
25 extent, but I think it's reproducible.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 CHAIRMAN MCGUIRE: Dr. Mustoe?

2 DOCTOR MUSTOE: Just one comment. I think  
3 in terms of Dr. Margolis's interesting study on wound  
4 closure, I think even more so photography is going to  
5 have, I think, a high degree of reliability in terms  
6 of necrotic tissue because necrotic tissue, unless  
7 somebody can tell me differently, is not pink or red.

8 CHAIRMAN MCGUIRE: Dr. Margolis?

9 DOCTOR MARGOLIS: I was involved, and this  
10 is all in published data, with some company that was  
11 trying to do a reliability study comparing photographs  
12 and human appearance for debriding agents and they  
13 were having an awfully hard time finding good  
14 reliability, so I would agree with you.

15 But one thing that needs to be understood  
16 is reliability studies are done to look to see how  
17 much agreement there is. And agreement is never, I  
18 shouldn't say never, hardly ever 100 percent. That's  
19 why the studies are done and that's why people  
20 interpret capitis and interrelated reliability  
21 coefficients in the ways that they do.

22 CHAIRMAN MCGUIRE: Dr. Lavin?

23 DOCTOR LAVIN: Yes. I think with these  
24 wound care agents, my sense is that unless the end  
25 point is, you know, complete healing they probably

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 belong in a different guidance document.

2 CHAIRMAN MCGUIRE: How do you like that?  
3 Tell me, does the committee want to deal with topical  
4 analgesic agents which are going to be subjectivel y  
5 analyzed? Topical antimicrobial agents which could b e  
6 analyzed by culture? Wound deodorizing agents which  
7 you'll admit is subjective and others?

8 Dr. Drake?

9 DOCTOR DRAKE: I'm now confused, I' m  
10 sorry, I'm going to go back prior to your comment to  
11 what Lavin said. I thought that one of the arguments ,  
12 and this is again I'd be interested in what the FD A  
13 folks heard, because what I thought we heard is that  
14 there was diversity among the committee that 10 0  
15 percent healing is not a reasonable endpoint, at least  
16 that was my personal opinion, I did hear it echoed by  
17 some others, and yet you just said to have 100 percen t  
18 healing input, and so now I'm really interested. I  
19 mean I think this process is fascinating. I'd be ver y  
20 interested in what you guys heard.

21 DOCTOR WEISS: You're probably going t o  
22 hear six different things from the six of us. What I  
23 heard, and this happens a lot, not in just this kind  
24 of product or this kind of a condition, but lots o f  
25 other things. Should the agent do what it says it's

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 supposed to do, or should there be a more, something  
2 that's maybe a more harder endpoint, but more of a  
3 measure of clinical benefit, and that's what we were  
4 addressing just now with the last several minutes of  
5 discussion. Is it enough to say something debride s  
6 the wounds, or should that debriding then translat e  
7 into faster healing, better healing, just as goo d  
8 healing, but easier to apply, something that's mor e  
9 patient benefit.

10 CHAIRMAN MCGUIRE: I think Dr. Drake has  
11 gone a bit further than that. Dr. Drake has gone bac k  
12 to wound closure I believe.

13 DOCTOR DRAKE: I mean I wanted to mak e  
14 sure that what Dr. Lavin said didn't indicate that th e  
15 consensus of this group was that you had to have 100  
16 percent wound closure in order for it to meet efficac y  
17 standards from the FDA because that would strongl y  
18 disagree with. I think 100 pe rcent of anything is an  
19 unreasonable standard, and I think it's detrimenta l  
20 and potentially could interfere with something, a ver y  
21 useful product, being made ava ilable to our patients.

22 I mean I would suggest to you tha t  
23 hypertension has yet to be cured, but nobody woul d  
24 suggest that there aren't antihypertensive medication s  
25 that are of a great benefit to the patient.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 CHAIRMAN MCGUIRE: Dr. --

2 DOCTOR DRAKE: And I guess that's true  
3 across the board in medicine. I think absolutes are  
4 very dangerous and I would hate to see this committee  
5 go forward with an absolute. If you took that forward  
6 in your opinion, then I wanted to express a dissenting  
7 opinion, that I think that that's not the correct way  
8 to proceed.

9 CHAIRMAN MCGUIRE: Dr. Lavin, Dr. Drake  
10 has some question about what your intention was with  
11 your remark?

12 DOCTOR LAVIN: Okay, throw it back to me.  
13 My sense is that when the chips in the end and  
14 everything is looked at, what's the easiest endpoint  
15 to look at. I do think 100 percent healing is the  
16 easiest endpoint to look at.

17 And my other concern in why I made the  
18 original comment is that I'm just concerned that if  
19 these, you know, issues related to these wound healing  
20 agents aren't defined up front, then you're going to  
21 have a lot of heterogeneity in your studies and you're  
22 going to have real difficulty, you know, analyzing  
23 this debridement that we talked about this morning in  
24 terms of the portions we have debridement, and then  
25 you have proportions of debridement with methodology

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 A, proportions that have debri dement with methodology  
2 B, and we're right back to what, you know, Clie n t  
3 Miller was saying this morning.

4 And my concern is we want to t ry to avoid  
5 those kind of situations where we have all these mixe s  
6 and matches and combinations and permutations, keep i t  
7 clean and keep it simple. And if 100 percent healing  
8 is the step in that direction, then that's what I' m  
9 behind.

10 CHAIRMAN McGUIRE: Go ahead, Dr. Drake.

11 DOCTOR DRAKE: Well, I think i t's a nobel  
12 sentiment spoke like a true epidemiologist an d  
13 statistician who wants to deal in absolutes, but I  
14 deal in patients, and I am really opposed to sayin g  
15 that something has to be absolute before it get s  
16 approved by the FDA.

17 I mean if something shows a benefit to a  
18 patient in terms of rate or improvement and healing o r  
19 progress for the patient or enables the wound to b e  
20 covered, as the gentleman I th ink from New Jersey who  
21 has covered a lot of wounds suggested, then I'm al l  
22 for it. I don't think we should preclude product s  
23 from getting out to our patients that might be o f  
24 benefit to them in a variety of way.

25 And to set a standard just bec ause it's a

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 nice end point to measure, I mean medicine is no t  
2 perfect. Patients don't all behave the same way .  
3 It's an impossible standard --

4 MR. CLINTON MILLER: First of all don' t  
5 indict all epidemiologist and biostatisticians --

6 DOCTOR DRAKE: But you guys like clean data and I  
7 understand that, but I can't always give you clea n  
8 data as a clinical investigator because sometimes --

9 MR. CLINTON MILLER: -- I'm not arguin g  
10 with you --

11 DOCTOR DRAKE: -- there's not a perfec t  
12 endpoint --

13 CHAIRMAN MCGUIRE: Wait, wait.

14 Dr. Miller, did you have a comment?

15 MR. CLINTON MILLER: Yes, I do. I don't  
16 believe I at any point propose d the perfect endpoint.  
17 In fact I had been arguing against that. I've bee n  
18 arguing that it's a multi-dimensional set o f  
19 endpoints. And I believe that you never saw a label  
20 on a drug that says "this cures," you say "i t  
21 enhances." That's the way they all come out.

22 And while we're talking about enhances th e  
23 closure or etcetera, the other thing is that we d o  
24 have to remember that if you're given choices o f  
25 arriving at any endpoint, whet her or not it's a total

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 closure or partial or whatever it is, the amount o f  
2 resources that you would spend to get to tha t  
3 endpoint, whatever it is, can and will be differen t  
4 and therefore rates of closure do come in to it. And  
5 I don't believe that Dr. Lavin was serious when h e  
6 said we need another document, I think he was jus t  
7 teasing us.

8 CHAIRMAN MCGUIRE: If I could, we had a  
9 long and full discussion of endpoints earlier today,  
10 and I thought we went though it in some detail, an d  
11 the Agency indicated that they had a good notion o f  
12 the consensus and the differen ces of opinion on ulcer  
13 closure.

14 We've discussed ulcer recurrence. We wer e  
15 beginning to discuss debriding agents, and I think we  
16 finished that discussion. And then we have thes e  
17 other four agents, wound deodorizing agents, topical  
18 antimicrobial and topical anal gesics, and do you want  
19 to discuss them singly or do you want to apply th e  
20 same criteria to them, if it works, it works, and it  
21 will be a subjective analysis except for th e  
22 bacteriology. And you would like to know, you would  
23 like some indicators if they h ad a deleterious affect  
24 on healing?

25 Yes, Dr. Lipsky?

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DOCTOR LIPSKY: I'd like to have a dissen t  
2 for topical antimicrobial agents. I think relieving  
3 pain nobody would argue with. And probably removing  
4 odor nobody would argue with. But what is th e  
5 clinical advantage to killing bugs? The patien t  
6 doesn't know the difference, and I'm not sure that th e  
7 wound knows the difference. So I think at least for  
8 that one, because it's being done as a surrogate or a s  
9 a hope that you will have anot her beneficial endpoint  
10 (i.e. wound closure), then you need to prove that, and  
11 I think at least in the case of the neuropathi c  
12 diabetic foot ulcer that's not been proven.

13 CHAIRMAN MCGUIRE: Okay, Dr. Lipsky i s  
14 putting on the line the efficacy of topica l  
15 antimicrobial. And if such a thing is brought to the  
16 Agency we'd have to have demonstrated efficacy, i s  
17 that fair?

18 DOCTOR MARZELLA: Or for an additiona l  
19 benefit, decreased infection.

20 DOCTOR LIPSKY: Right. I woul dn't have a  
21 problem with an agent that was used to say that this  
22 topical antimicrobial either cured infections compare d  
23 with a systemic antimicrobial or no antimicrobial or  
24 it aided in wound healing when compared with no use o f  
25 an an antimicrobial. But just decreasing the colony

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 counts to me is of no value.

2 CHAIRMAN MCGUIRE: Okay, Ms. Cohen?

3 MS. COHEN: I have a question of Dr .  
4 Cooper. In terms the patients that you see, what are  
5 their expectations, what do they say, what are the y  
6 looking for in terms of their wounds?

7 DOCTOR COOPER: That their wounds b e  
8 healed.

9 MS. COHEN: They want to be he aled. Now,  
10 what does healing mean to them?

11 DOCTOR COOPER: I think it means that it  
12 doesn't keep recurring and it's not there for year s  
13 and years, and it's a bother t o them and it distracts  
14 them from other things, and it's emotionally draining ,  
15 and frequently it makes them not be able to do other  
16 things in their lives.

17 MS. COHEN: Okay. My concern I guess, an d  
18 I wanted to know that, is if you allow someone t o  
19 manufacture this cream, how are you going to control  
20 what they're going to say about it, and does it make  
21 that much difference? Someone mentioned doin g  
22 debriding, someone mentioned moisture pack, what are  
23 you going to get out of this that you don't alread y  
24 have anyway? So you're looking for something that's  
25 going to be as efficacious as possible, and if it' s

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 kind of well it might, it might not, I can just see e  
2 the media and I can see the advertising practices with h  
3 that cream. So I think you have to be more e  
4 definitive. And that's the endpoint in what consumers  
5 are going to believe it does.

6 CHAIRMAN MCGUIRE: Do I have the  
7 permission of the Advisory Committee to go into item  
8 five which is definition of acceptable closure?

9 DOCTOR COOPER: Yes.

10 CHAIRMAN MCGUIRE: Okay, let me --

11 DOCTOR ROSENBERG: I'd like to just raise  
12 one more issue?

13 CHAIRMAN MCGUIRE: Okay, wait, who is  
14 first?

15 DOCTOR ROSENBERG: I'm sorry.

16 CHAIRMAN MCGUIRE: Dr. Rosenberg, go  
17 ahead.

18 DOCTOR ROSENBERG: We're talking about t  
19 ulcers and wounds. Let me back up a little bit .  
20 We've talked about only three kinds of ulcers, this is  
21 yesterday and so far today, we've talked about the e  
22 neutrophic and the diabetic, which was a specific  
23 indication. We've talked about the stasis, the venous  
24 dependent leg ulcers, and we've talked about the e  
25 pressure ulcers, the decubitus.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           Much of the research in ulcers and in skin  
2 healing and in wound healing has been done by nature  
3 of the experimental system with acute wounds and acute  
4 ulcers. I know that Dr. Eaglstein has spent many years  
5 doing that, and I know Dr. Mustoe talked about it, but  
6 there are acute wounds that occur and acute ulcers and  
7 there are traumas. And in terms of, it's not the  
8 chronic problem, but it's a very frequent problem.  
9 And in terms of the task of the Agency, there are  
10 people that want products for those indications and  
11 the Agency has got to review them. And I think, I'm  
12 not sure that we're not limiting ourselves too much to  
13 these things and which something else is causing the  
14 skin to break down, and I certainly more than anybody  
15 else has kept saying that it's that initial cause we  
16 should be thinking about and not the skin.

17           And just, like a terrier, to go back to  
18 PDGF, are there data showing that PDGF is very  
19 effective in acute wound healing where there is no  
20 underlying something else --

21           CHAIRMAN MCGUIRE: Dr. Rosenberg, wait --

22           DOCTOR ROSENBERG: -- other agents or any  
23 of these things that we're talking about.

24           CHAIRMAN MCGUIRE: -- I want to hear from  
25 the Agency in just a minute, but the idea that we can

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 cover these three major forums of chronic ulcers in a  
2 day is really staggering. I mean I think that wa s  
3 very ambitious and I hope that after I leave thi s  
4 afternoon and I get on a plane that you all finis h  
5 sometime tonight.

6 Acute wounds are different enough fro m  
7 what we're dealing with that the Agency is going t o  
8 deal with it as a separate issue. And so while I  
9 agree with Dr. Rosenberg, it's an important problem or  
10 it's an important issue, it will be dealt with.

11 And, Bill, if you could just let me ge t  
12 through this, I would like to get into this item five  
13 and finish with it.

14 "The definition of acceptable closure and  
15 durability of closure may be d ifferent for grafts and  
16 skin substitutes. Partial healing, if measured b y  
17 predetermined criteria, coupled with successful g  
18 rafting to achieve complete healing might b e  
19 reasonable as a measure of clinical benefit. Complet e  
20 closure (epithelialization) that is achieve b y  
21 successful application of a bioengineered ski n  
22 substitute might also be a measure of clinica l  
23 benefit.

24 "How should one best define the acceptabl e  
25 criteria for wound healing, for grafts an d

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 bioengineered skin substitutes? Is closure of a n  
2 ulcer by "take" of a bioengineered skin substitute a  
3 valid surrogate for healing? What criteria, fo r  
4 instance durability, function, should be used a s  
5 indication of clinical benefit ? What is the value of  
6 assessment of "epithelial sheen" in determining th e  
7 take of the product? For surgical grafts and ski n  
8 substitutes, please discuss at what time point post-  
9 grafting "take" can be assumed to have occurred."

10 Okay, this is an entirely diff erent issue  
11 than we have been dealing with today, although we hav e  
12 referred to it and we've alluded to the issue that a  
13 bioengineered product might then permit one to place  
14 an algenaic keratincytes product or some other final  
15 closure, but we're in new territory now and I think we  
16 can start.

17 It's 20 of 3:00, and I think we shoul d  
18 discuss this for a while and t hen have a break before  
19 we go on to the next part of the afternoon.

20 Would anyone like to take on th e  
21 bioengineered products? Doctor Mustoe.

22 DOCTOR MUSTOE: I don't in any way want t o  
23 take it on in totality because it's a complicated are a  
24 but I do think there's a critical issue abou t  
25 durability that has be conside red with skin grafts or

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 tissue engineering. I think that the amount of effort  
2 that goes into a graft. For instance, in terms of --  
3 morbidity is higher, certainly in terms of tissue  
4 engineering may be higher. But the problem is that it  
5 takes a long time and it can be very variable  
6 depending on the product for desmosomes and anchoring  
7 fibrils basically to be resistant to shearing forces.  
8 And a skin graft that has an epithelial covering that  
9 is totally susceptible to shearing is not necessarily  
10 a very valuable product and that's certainly been an  
11 issue for, for instance, on the burn patients on some  
12 of these products.

13 So I think that much more so it may seem  
14 like a higher standard but I think it's appropriate  
15 that durability, in other words, some real attention  
16 to a one month, two month, three month follow-up --  
17 I'm not sure how long -- to state that the product is  
18 durable has just got to be a part of it or otherwise,  
19 I think you're going to have a product that shears off  
20 with minimal trauma hasn't done very much.

21 CHAIRMAN McGUIRE: Okay. That's the  
22 doomsday view of it, and I'll give a little more  
23 upbeat view of it. I think there have been grafting  
24 procedures using autologous keratinocytes in which, to  
25 be sure, the result was quite fragile. But there is

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 a maturation and eventually formation of anchorin g  
2 fibrils and a more or less functional basemen t  
3 membrane. And periodically in the burn literature one  
4 discovers a case report of an autoimmune blister and  
5 that really represents the fragility of the basement  
6 membranes for many months. Many months. So we'r e  
7 talking about -- if we're talking about grafting ,  
8 we're not talking about the equivalent of a spli t  
9 thickness skin graft or full thickness skin graft.

10 DOCTOR MUSTOE: No. I'm not saying in a  
11 doomsday that they don't have value. I'm just simply  
12 saying that the durability becomes particularl y  
13 relevant. That's all. That how resistant they are t o  
14 minor shearing forces has to be considered.

15 CHAIRMAN MCGUIRE: Correct. I agree, and  
16 I think that's a function of time.

17 Yes, Doctor Margolis.

18 DOCTOR MARGOLIS: I don't thin k it's even  
19 as easy a question as that because I don't think the  
20 mechanism of how some of the allografts or even a  
21 split thickness skin graft works. I think sometimes  
22 you may graft a wound and the graft may look like it' s  
23 no longer taken or it may even be fully sloughed off  
24 and then the wound may go on to heal and it may heal  
25 faster than in the other cases because the graft i s

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 secreting growth factors or doing something which is  
2 helping the wound.

3 I think, although for the first take  
4 durability becomes very important and that you might  
5 want to make sure that it's in place for two, three,  
6 four, whatever the magic number of weeks is. But I  
7 think if the wound just goes on to heal and the graft  
8 is already sloughed off you shouldn't ask any  
9 different durability question of that ultimately  
10 healed wound in what's no longer the presence of the  
11 graft than you would have of any other recombinant  
12 PDGF treated wound or anything else. So I almost feel  
13 like you need two definitions of healing in those  
14 patients.

15 CHAIRMAN MCGUIRE: Let me reiterate what  
16 I heard and you tell me if I heard what you said .  
17 That in the case of autologous keratinocyte grafting,  
18 engraftment of the keratinocytes may not be the only  
19 benefit of the graft, that you can promote healing  
20 even though there is not retention of the allogeneic  
21 graft as demonstrated by DNA analysis, etcetera ,  
22 etcetera.

23 DOCTOR MARGOLIS: I think that 's probably  
24 true.

25 CHAIRMAN MCGUIRE: Is that pretty much

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 what you said?

2 DOCTOR MARGOLIS: Yes. I think that if  
3 you want to say that the graft itself has caused  
4 healing, then I agree absolutely with everything  
5 that's been said including what Doctor Eaglstein  
6 started about an hour ago, is that you need to make  
7 sure that graft stays in place for several weeks.  
8 What often happens -- again talking about my practice  
9 -- is that I end up seeing a patient who was grafted  
10 by a plastic surgeon and said the patient was  
11 quote/unquote "healed" and now it's three weeks later  
12 and the patient has a nice open leg ulcer.

13 So I agree that's a problem but I also  
14 think that grafting itself does something to the wound  
15 and that wound that may heal after the graft is  
16 already no longer present shouldn't be evaluated any  
17 differently than all these other wounds that we're  
18 talking about.

19 CHAIRMAN MCGUIRE: I just wanted to make  
20 sure that everyone understood you were talking about  
21 allogeneic grafts.

22 Doctor Eaglstein had his hand up.

23 DOCTOR EAGLSTEIN: I wanted to follow on  
24 what Doctor Margolis was just saying. I've had  
25 personal experience with one product that has a n

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 epidermis and a dermis and doesn't have as difficult  
2 a time getting the anchoring fibrils being as durable  
3 as the epithelium alone. In this case with this  
4 product, what we see is sometimes it works just the  
5 way he said. It's clear that the product doesn't  
6 stay, doesn't seem to really take or engraft or become  
7 a permanent part of the skin but it stimulates the  
8 ulcer to heal. So that's one type of healing that it  
9 induces.

10 But other people with the same product and  
11 the same ulcer type seem to have the graft take and  
12 this is foreign material and you can see that it's a  
13 graft. You can see that it's not the person's own  
14 skin. It looks like the graft you put but it looks  
15 alive and it tends to be alive and some of them just  
16 go ahead like that until later you can't tell. You  
17 can't tell if it's what you put there or if silently  
18 the body replaced it. And I think that poses, to me,  
19 not a problem but I think that should just be called  
20 healing. That's just a different pattern of healing  
21 than we've ever seen. It's really the pattern we  
22 might be after. We would really probably prefer that  
23 we could make an off-the-shelf skin, put it in an  
24 ulcer and soon we couldn't tell whether it was the  
25 patient's skin or what we put there. But I think

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 that's never been reported before and the agency is  
2 asking for advice on how to grade that sort of  
3 healing.

4 So I think there's at least these two  
5 patterns or a mixture of them. The pattern Doctor  
6 Margolis pointed out where you know the tissue you put  
7 there isn't still there but somehow now the ulcer  
8 heals may be because that tissue made products or made  
9 cytokines or growth factors. And then there's the  
10 pattern where the tissue seems to be there and  
11 sometime later you can't tell if it's the tissue you  
12 put there or the patient's own skin and then there can  
13 be an intermediate stage where a little piece seems to  
14 fail but another part seems to take.

15 CHAIRMAN MCGUIRE: I think all of us have  
16 seen examples of xenografts and also allografts that  
17 were meshed and then months later the skin had healed  
18 and still had retention of the mesh pattern. Most of  
19 those observations are made at a time when DNA  
20 analysis wasn't available and I think what the agency  
21 is asking for us now is not whether we should be  
22 developing products or we should be reviewing products  
23 but whether our criteria of take of the product, of  
24 the bio-engineered product, whether it's allogeneic or  
25 autologous and whether the dermal equivalent contains

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 your fibroblast, the patient's fibroblast. They want  
2 to know how to look at it, how to analyze it. What  
3 are the criteria for success?

4 DOCTOR EAGLSTEIN: That's what I think and  
5 I would like to say, as I said before, I think you  
6 should ask for a -- this is a time when you'd like to  
7 see on those that you said are taking that they stay  
8 there for a period of time, a few weeks or a month .  
9 Not many months but a few weeks or a month. But that  
10 would be in the second pattern.

11 The first pattern they clearly don't seem  
12 to take yet they -- they, those bio-engineered tissue s  
13 -- induce healing. I think the advanced tissue  
14 sciences people might report a different pattern with  
15 a dermal product that they have.

16 CHAIRMAN McGUIRE: There's a question  
17 behind you. Thanks, Doctor Eaglstein. Yes.

18 MR. ALVAREZ: I would just like to just  
19 echo that because we saw three patterns in our  
20 experience with bio-engineered skin. We saw healing  
21 by the host and we thought that efficacious because we  
22 saw ulcers that weren't healed for 20 years heal in  
23 five months and we thought that was pretty good.

24 We also saw this take, this frank  
25 permanent take that we called permanent because we saw

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 it all throughout the study period. And then we saw  
2 another special event we call persistence where the  
3 actual material remained on top of the wound as an  
4 epidermal cover without leakage. However, if you  
5 examined carefully, there was still wound or perhaps  
6 like a blister roof but it looked fairly permanent .  
7 So you have these three different appearances that  
8 needed to be measured very carefully because we do  
9 think there's efficacy in all three of those ways.

10 So I think for bio-engineered skin, it's  
11 important for the agency to realize that these  
12 products do behave in a unique fashion that we have  
13 yet not been able to measure completely.

14 CHAIRMAN McGUIRE: Okay. The product  
15 you're talking about contained allogeneic, fibroblast  
16 and allogeneic keratinocytes?

17 MR. ALVAREZ: Yes.

18 CHAIRMAN McGUIRE: Okay. And could you  
19 tell by visualization without biopsy what had taken,  
20 what was persistent, what had --

21 MR. ALVAREZ: Oh, sure. You could tell.  
22 You could the difference between persistence and frank  
23 healing. Absolutely. And you could also tell the  
24 difference when it was behaving as a dressing. But it  
25 took a little bit of clinical experience to gather

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 that, the first couple of patients.

2 CHAIRMAN McGUIRE: And in the grafts that  
3 had healed, whose DNA was in that biopsy?

4 MR. ALVAREZ: We don't know the answer to  
5 that. It wasn't done in the study.

6 CHAIRMAN McGUIRE: There's another  
7 question for you.

8 DOCTOR BERGFELD: It seems to me as I  
9 listen the end point still is healing, but you are  
10 dealing with is a delayed healing, a judgment.

11 MR. ALVAREZ: Yes.

12 DOCTOR BERGFELD: But what would be that  
13 period of time?

14 MR. ALVAREZ: I agree with Doctor Mustoe,  
15 Doctor Eaglstein, and Doctor Margolis that when there  
16 is this frank take which should definitely be measured  
17 in some way, there ought to be a persistence or an  
18 endurance where you have to call it completely healed  
19 clinically like for four weeks in a row.

20 DOCTOR BERGFELD: So you're eight weeks.

21 MR. ALVAREZ: Well, you know, the first  
22 time you see it take --

23 DOCTOR BERGFELD: -- to a time period.

24 MR. ALVAREZ: Right. When you first see  
25 a take, you should be able to call it healed four

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 weeks in a row as opposed to when you get, fo r  
2 example, healing by secondary intention. We thin k  
3 this is speeding healing. Maybe you don't need t o  
4 follow it as long. Maybe you need to call it healed  
5 two times in a row.

6 DOCTOR BERGFELD: So you're basically at  
7 three months.

8 MR. ALVAREZ: Oh, yes.

9 DOCTOR BERGFELD: Until your healed time  
10 for whatever mechanism that you --

11 MR. ALVAREZ: I think three months i s  
12 necessary.

13 CHAIRMAN MCGUIRE: Other questions fro m  
14 the committee? Yes, Doctor Hashimoto.

15 DOCTOR HASHIMOTO: I just wonder i f  
16 recovery of sensation comes together with this graft  
17 like a peripheral nerve. Tactile sensation, -- cell  
18 recovery. If sensation is not there, mayb e  
19 traumatized --

20 CHAIRMAN MCGUIRE: I suspect s omeone here  
21 knows that. I know for sure that the Longerhans cell s  
22 reenter the autologous keratinocyte grafts.

23 I may not have asked the agency' s  
24 questions in a very clear fashion.

25 DOCTOR MARZELLA: We are happy with what

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 we have heard.

2 CHAIRMAN MCGUIRE: Are we finished with  
3 five? I'm sorry. You've tried to ask your question  
4 twice. We're finished with question five after you  
5 sit down. That's what I meant.

6 DOCTOR BARBUL: I would just like the  
7 panel to give a slight historical view again. The  
8 skin substitutes begin their life in situations where  
9 autologous skin was not available and in initial  
10 approval and clinical use they were granted, if you  
11 will, the use in a situation which was desperate. Now  
12 we're talking use in situations where autologous skin  
13 is available, and I would recommend that perhaps as a  
14 starting study they be compared to autologous split  
15 thickness or full thickness skin grafts in  
16 performance, end points, healing and so forth which I  
17 think is important because the cost is a factor and  
18 performance and all these issues come into play and  
19 they need to be compared with available skin that the  
20 host has.

21 CHAIRMAN MCGUIRE: Okay. Thank you.  
22 There are two speakers from the public and I propose  
23 that we receive their information and then have a  
24 break. The speakers are Diane Krasner.

25 MS. KRASNER: Diane Krasner from Baltimore

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 University of Maryland. I just have four brief  
2 comments. Most of them are responses to issues that  
3 came up this morning.

4 The first is that in order to design  
5 research protocols that are acceptable to IRBs and  
6 that result in trials that are hopefully clinically  
7 relevant, I would suggest that the panel and the  
8 agency ascertain that the guidance document is  
9 consistent with AHCPR guidelines for pressure ulcers  
10 and that perhaps you even consider looking at other  
11 generally accepted community standards of care such as  
12 the new venous ulcer guideline from the University of  
13 Pennsylvania.

14 I think it's important that if we go into  
15 clinical settings to do clinical trials that we not  
16 get caught in a bind of the AHCPR having set one  
17 standard, this agency setting another, HCFA setting  
18 another and those of us that are tearing out the  
19 protocols finding ourselves in terrible dilemmas.

20 My second point concerns the discussion of  
21 leg ulcers this morning and I have serious concerns  
22 that it did not reflect the community standard of care  
23 and the research literature, especially with regard to  
24 the variability of compression therapy options  
25 required for optimal care and the issue of serial

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 debridements, and I respectively submit that th e  
2 discussion I heard doesn't reflect what I believe is  
3 the national and the international standard and I  
4 would hope that you would look at those issues more.

5 The third --

6 CHAIRMAN McGUIRE: Excuse me. Could you  
7 amplify a bit. I heard compression and I hear d  
8 debridement. There's something you didn't hear.

9 MS. KRASNER: Well, what I did n't hear is  
10 regard for the different types of compression tha t  
11 need to be carefully considered and that thos e  
12 variables then that would enter into the stud y  
13 designs. And concerning debridement, what I heard wa s  
14 a consensus here that an initial debridement, goo d  
15 debridement was the standard, perhaps with som e  
16 follow-up debridements and in, for example, th e  
17 largest applied algorithm in this country in th e  
18 franchised wound centers, 120 franchised wound center s  
19 in the country, that's not a part of their treatment  
20 algorithm. Their treatment algorithm is continuou s  
21 serial debridement for venous ulcer patients. So I  
22 think those things just have to be considered as you  
23 make a decision about that issue.

24 The third point concerns dressings and th e  
25 whole issue of moist wound hea ling as the standard of

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 care and I think that a definition of moist wound  
2 healing should be -- you should strive to develop a  
3 standard definition that reflects perhaps standard  
4 understanding. So, for example, unabsorbable moist  
5 dressing experts is not considered moist wound  
6 healing. The problems raised with that gold standard  
7 of normal saline is that unless you carefully monitor  
8 the dressing frequency to assure that it doesn't dry  
9 out, your gold standard has in fact become a dry gauze  
10 dressing. So there have to be careful criteria in  
11 terms of it being a real moisture retentive dressing  
12 as a control.

13 Another point concerning dressings is that  
14 let's say you're evaluating a dressing because your  
15 end point is achieved absorption. That's the whole  
16 point of development of this particular dressing or  
17 product. Then normal saline moist dressings wouldn't  
18 be the appropriate control and so that may need to be  
19 a flexible variable in the control arm of your design,  
20 depending on what your outcome is.

21 And finally I would just like to close  
22 with a plea to both the panel and to the agency that  
23 you continue to seek the input when developing this  
24 guidance document of the major wound healing  
25 organizations, all of whom are represented today in

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 this room and hope to continue to be part of thi s  
2 process. Thank you.

3 CHAIRMAN MCGUIRE: Thank you very much ,  
4 and I'm sure the agency will.

5 Does anyone on the panel want to defen d  
6 himself or herself or make any comments?

7 DOCTOR MUSTOE: I would just make on e  
8 comment. I think that many of the things you said I  
9 think probably we would agree with. It's a matter of  
10 interpretation, but it disturbs me when I hear tha t  
11 120 wound centers around the c ountry are using serial  
12 debridement for venous ulcers with the implicatio n  
13 that's the standard of care. I would vehementl y  
14 disagree that that is the standard of care. I would  
15 simply question. I think that 's one of the issues of  
16 wound care in general is is that there are multipl e  
17 reasons for why people do things. Economic incentive s  
18 unfortunately can play a role and that's nowhere more  
19 true than in debridement and one of the issues o f  
20 defining debridement is when I pick off a crust, i n  
21 some people's hands I'm sure that's debridement an d  
22 certainly when you're doing a CPT code that may very  
23 well influence it.

24 At any rate, I just don't think seria l  
25 debridement of venous ulcers -- I don't think thi s

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 panel is -- I think we are representative of th e  
2 country. That's not the standard of care.

3 DOCTOR ROSENBERG: I would like t o  
4 associate myself with Doctor Mustoe's remarks.

5 CHAIRMAN McGUIRE: Ms. Cohen.

6 DOCTOR COHEN: What are these woun d  
7 centers? Are they like weight loss centers? I wish  
8 someone could tell me what they are. I mean I di d  
9 some of the work on weight loss centers so I'd like t o  
10 know what these wound clinics are. Are they staffed  
11 by physicians? Who's in charge?

12 CHAIRMAN McGUIRE: Could you --

13 MS. KRASNER: Let me make a comment.

14 CHAIRMAN McGUIRE: Let's make a brie f  
15 comment about the franchised wound care center.

16 MS. KRASNER: Right. There are franchise d  
17 wound centers that were started by a company, Curativ e  
18 Technologies out of New York. But the work and th e  
19 development of their algorithm was in fact, as yo u  
20 know, Doctor Mustoe, supported by the research done by  
21 Doctor Knighton who believes the serial debridement i n  
22 fact perhaps stimulates the release of endogenou s  
23 growth hormone and in fact promotes wound healing .  
24 He's written extensively. You may or may not agre e  
25 with the algorithm but I'm just saying the algorithm

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 is out there and it's in large use in large numbers o f  
2 patients and those become issues that need to be a t  
3 least considered, I believe, when one looks at th e  
4 development of a guidance document. That's all I' m  
5 saying.

6 CHAIRMAN McGUIRE: Okay. Thanks ver y  
7 much. I certainly do not --

8 DOCTOR COHEN: I would like to know --

9 CHAIRMAN McGUIRE: Lynn, I really don' t  
10 want to get into an evaluation of the franchis e  
11 program.

12 DOCTOR COHEN: Are they licensed?

13 CHAIRMAN McGUIRE: That's fair. But I  
14 think all of our speakers have filed COI statement s  
15 with the agency. Is that correct? Okay. I think th e  
16 question that came up from the panel is have ou r  
17 speakers filed a conflict of interest statement with  
18 the agency and, if you haven't, please do.

19 MS. RILEY: Would you please s tep and say  
20 who paid your expenses and who you're affiliated with  
21 so that we'll know.

22 MS. KRASNER: My name is Diane Krasner an d  
23 I'm a doctoral student at the University of Maryland  
24 School of Nursing. I happen to know about th e  
25 franchise wound centers because I've done m y

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 dissertation research there on pain in venous ulce r  
2 patients for the last two year s. I also happen to be  
3 a part-time executive director of the Association for  
4 the Advancement of Wound Care and they paid m y  
5 expenses to be here today but I'm not representin g  
6 them in my comments. My comments were just made a s  
7 me, clinical nurse from Baltimore.

8 CHAIRMAN MCGUIRE: Thank you very much .  
9 Is Doctor Harlin here?

10 DOCTOR HARLIN: Good afternoon. My name  
11 is Doctor Stephen Harlin. You have two pieces of wor k  
12 from me. One is an article, actually a manuscrip t  
13 recently submitted for publication and not ye t  
14 accepted, so to protect exclusivity, please do no t  
15 share this or publish it. It's supplied to you simpl y  
16 to support my comments to you today.

17 Basically, why I am here. First of all,  
18 I am a reconstructive plastic surgeon and I practice  
19 in Philadelphia. I hold an academic affiliation and  
20 have affiliations with three suburban communit y  
21 hospitals in Philadelphia. My practice is devoted ,  
22 unlike most plastic surgeons in Philadelphia, m y  
23 practice is devoted almost exc lusively to wound care.

24 I see on average about 500 non-healin g  
25 wounds per year, so somewhere around 40 new wounds pe r

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 month. The patients that I see are the toughest  
2 wounds around. I get the patients that are in that 20  
3 percent of the chronic wound population who, despite  
4 strict attention to fundamentals and very careful  
5 technique and good intentions, still fail to heal.  
6 The name of my practice is the Wound Clinic. It's a  
7 small group of individuals, five, and has no franchise  
8 and no connection financially with anyone.

9 The reason I'm here is the following. I  
10 have to give a talk in San Francisco next month before  
11 an international congress on the subject of  
12 angiogenesis growth factors in the non-healing wound  
13 and so about three months ago I went to the library to  
14 try and find every single article written on the  
15 application of exogenous growth factors to chronic  
16 wounds. It took about three months, a lot of digging.  
17 Finally decided I had everybody's article, many of  
18 which are written by some of the pioneers which are in  
19 my midst.

20 When I thought I had everybody's article,  
21 I then took my McIntosh and created a database and  
22 just tore all the articles apart and just data piece  
23 by data piece filled in data fields. When I thought  
24 I had everybody's article in and torn apart, I started  
25 asking the database questions such as how many - -

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 first of all, I defined what i s a well designed trial  
2 and that's in the article. I'm not going to repea t  
3 that now. I started asking the database in wel l  
4 designed trials, how many pati ents actually completed  
5 well designed trials and were found to have a n  
6 efficacious result as defined by the authors and saw  
7 that when we started separating things out, som e  
8 pretty interesting numbers appeared. You've got all  
9 that. It's in that article.

10 When I sent that to Doctor Stromberg, he  
11 sent me back a list of questions which you're al l  
12 dealing with now and so I tried to answer every one o f  
13 those questions that you're here to do and basically  
14 I went to the literature, the kind of thing that we d o  
15 in my practice, to try and get you answers. Thos e  
16 answers are all in this piece and this is no t  
17 submitted for publishing so you can do anything yo u  
18 want with this.

19 I just wanted to say a couple of thing s  
20 bottom line about this piece. First of all, as fo r  
21 defining standards of wound care, I think tha t  
22 standardized care regimens are probably one of th e  
23 most urgent requirements we as a group of wound care  
24 practitioners. Although protocol based wound car e  
25 might appear infeasible because wounds are s o

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 heterogeneous, I think that well designed clinical  
2 trials which maintain meticulous records of pertinent  
3 wound parameters and utilize what are called best  
4 standard wound care techniques can be developed.

5 As for managing all the co-variables and  
6 confounding factors in clinical trials in wound  
7 healing, I think that enrolling every patient with a  
8 chronic wound, then gathering comprehensive  
9 information, calculating the strength of associations  
10 and then translating clinical factors which appear  
11 strongly related to outcome into practice is the way  
12 to go. That's what we're doing in my practice. For  
13 four years we have taken patients and measured  
14 everything we can possibly measure on them and put all  
15 of that into a database.

16 So now we have a lot of patients and a lot  
17 of data and in the same way that I looked at the  
18 literature, we're now looking at that data and just  
19 asking it questions and I think that's valuable. I  
20 think if you try and measure everything and enroll  
21 everybody that results will come out of that.

22 One more comment on debridement. I know  
23 everybody's said a lot about it. One thing I haven't  
24 heard and that is that debridement is an operation.  
25 Operations cause pain. Operations carry risk.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Operations require informed consent. Operation s  
2 should be undertaken under anaesthetic and I think a  
3 lot of debridements are done without that. I hear a  
4 phrase around the hospital called bedside debridement s  
5 and I think that some of the debridements that ar e  
6 performed are bordering on cru el and that debridement  
7 has to be considered a real operation.

8 Just one final point and that as fo r  
9 partial healing and end points, I think that there ar e  
10 probably greater reasons to measure the journey than  
11 the destination. In my own patients, I see a lot of  
12 patients that never heal but p artially heal and I can  
13 tell you that there are benefits to either enhancing  
14 healing and not arriving at a totally epithialize d  
15 wound. There are benefits. Those include -- an d  
16 those are in your piece -- for many patients a n  
17 earlier return to function. If you can take a bi g  
18 wound and make it small, it mi ght get you functioning  
19 better. A reduction in the infectious threat which i s  
20 posed by portals of entry when you have an open wound ,  
21 and that's a relative issue. If you can reduce th e  
22 amount of entry, I think that's better.

23 Reductions in chronic wound pain. Smalle r  
24 wounds . There are small wounds that hurt like th e  
25 dickens and I look at and they're pea sized and they

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 cause a lot of pain but in general larger wounds tend  
2 to cause a little more pain. Multiple wounds cause  
3 more pain. I think overall if you enhance healing  
4 you're going to reduce pain. A reduction in the  
5 number of surgical procedures. This is if you get a  
6 partial result. You may save someone from an  
7 amputation. You may save someone from repeated  
8 debridements.

9 Patient satisfaction. As a clinician  
10 dealing with patients and their families, I can tell  
11 you that some success is a good thing. And I think if  
12 we measured very carefully the journey, that that's  
13 where the real information is. And finally, something  
14 in this era when cost containment is becoming an  
15 issue, partial success can also result in reduced  
16 health care costs.

17 CHAIRMAN MCGUIRE: Thank you very much .  
18 You've given us a number of things to think about.

19 We're going to have a break now. We will  
20 reconvene here at 3:30 and Doctor Wilma Bergfeld will  
21 chair the rest of the afternoon's meeting. Thank s  
22 very much.

23 (Off the record for a 28 minute break at  
24 3:12 p.m.)

25 ACTING CHAIRMAN BERGFELD: I wonder if we

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 can all sit down. Can we all reassemble, please .  
2 Would you all sit down, please. We'd like t o  
3 reassemble and begin again. As Doctor Joe McGuir e  
4 stated, I am Doctor Wilma Bergfeld and I'll b e  
5 chairing the session until its end. We do have a  
6 couple of remarks that need to be made prior to going  
7 on with the questions and Doctor Bill Eaglstein ha s  
8 asked to make a statement. Bill.

9 DOCTOR EAGLSTEIN: Thank you, Docto r  
10 Bergfeld. I meant it as a remark rather than a  
11 statement. There was a time earlier on when we were  
12 talking about these wound care products rather tha n  
13 wound healing products and then there were a number o f  
14 categories that were outlined and then topica l  
15 antimicrobials was kind of tak en out in some respects  
16 by the comment that it didn't matter how many bacteri a  
17 were in a chronic wound. And I did want to comment o n  
18 that.

19 The Agency for Health Care Polic y  
20 Research, its guideline for chronic wound has bee n  
21 that if chronic wound isn't healing -- this is a  
22 pressure ulcer -- for I think it's two weeks, it migh t  
23 be four weeks, they recommend the use o f  
24 antimicrobials, so there is one group that ha s  
25 surveyed the literature in thi s area and I think that

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 got a B rating. You know, they rank their  
2 recommendations by A, B and C based on the literature  
3 supporting the recommendation. So I think there is  
4 some real literature supporting the idea that even not  
5 infected wounds that aren't healing will benefit by  
6 treating with antimicrobials.

7 There are other reasons. Some have been  
8 mentioned. For example, if you're going to have  
9 grafting, if you're going to graft one of those  
10 wounds, you definitely would like to reduce the  
11 microbial load. As was referenced earlier, the  
12 likelihood of the graft taking is much better if you  
13 reduce the load, and that seems to be well documented  
14 and well accepted.

15 Other categories of reasons that may not  
16 be as well documented but which I think clinical  
17 observations support are that you can in some cases  
18 reduce weeping by reducing the load. You might reduce  
19 bacterial odor and you might reduce the chance of  
20 cross contamination from one wound to another or from  
21 a wound to a patient.

22 So there are many reasons I think that we  
23 as clinicians want to reduce the bacterial load even  
24 though we don't think that will for sure -- you know,  
25 absolutely heal the wound and so I'd like the panel to

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 at least reconsider or not accept the notion anywa y  
2 that this indication, reducing antimicrobials, I woul d  
3 think it belongs where it was put by FDA, as a  
4 legitimate goal of wound care. And I've worked in th e  
5 area and I've represented this view before and bee n  
6 involved in a study that is being considered by th e  
7 agency now, so I have a deep familiarity with th e  
8 background to the question. I hope I've been clear.  
9 If you have some questions, I'll --

10 ACTING CHAIRMAN BERGFELD: That's fine .  
11 Doctor Lipsky, do you care respond or make furthe r  
12 remarks?

13 DOCTOR LIPSKY: Yes, I would. Thank you.  
14 I appreciate Doctor Eaglstein's remarks and I don' t  
15 disagree with the vast majority of what you said and  
16 I don't think it disagrees wit h what I actually said.  
17 What I alluded to was that each of the othe r  
18 parameters, reducing pain, reducing odor and so o n  
19 were in and of themselves useful parameters that could  
20 be looked at and would benefit the patient. The idea  
21 of just reducing the number of bacteria, on the other  
22 hand, doesn't necessarily benefit the patient and it  
23 hasn't in many instances, particularly in the diabeti c  
24 foot infection, been proven to benefit the wound.

25 So if one is to argue for agents tha t

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 reduce bacterial bioburden, then I think one has to  
2 demonstrate that there are end points that are of  
3 importance to the wound or to the patient in doing  
4 that. I actually asked Doctor Thomas earlier what the  
5 data was for decubitus ulcers or pressure sores  
6 because I'm not as familiar in that area. He referred  
7 me to a paper actually written by Doctor Alvarez. I  
8 was just looking to see if he's still here and perhaps  
9 he could address that issue.

10 So I've opted out of saying anything about  
11 that area because I'm not as familiar with that  
12 literature but I think the literature on diabetic foot  
13 infections is very limited and what few papers there  
14 are are not very well designed. They're certainly not  
15 popularly done double blind crossover trials, and  
16 they're mixed in their reviews as to whether  
17 antimicrobial therapy given to clinically uninfected  
18 wounds has any benefit. It may or may not and I would  
19 welcome trials looking at that, but just decreasing  
20 bioburden of organisms is not an end point that I can  
21 see at this point has been proven to be of value.

22 From the point of view of cross  
23 contamination, it's not the number of organisms. It's  
24 the kind of organisms you have so we have many  
25 instances where there are a large number of organisms.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Our oral cavity has 10<sup>9</sup> organisms but we don't worry  
2 about that except if there's a particular organism of  
3 high virulence so just a few vancomycin resistant  
4 enterococci in a wound for example would cause me to  
5 be very concerned but 10<sup>8</sup> -- negative staph wouldn't  
6 cause me to be concerned at all. So I don't agree  
7 with the issue of reducing bioburden because of  
8 concern about cross contamination.

9 DOCTOR EAGLSTEIN: But I guess you would  
10 agree on reducing specific agents if an antimicrobial  
11 did not --

12 DOCTOR LIPSKY: If an antimicrobial  
13 reduced weepage, if it reduced odor, if it reduced  
14 pain, if it was associated with improved healing, I'd  
15 love to have it available.

16 DOCTOR EAGLSTEIN: I meant specific  
17 microbes, organisms that you felt would be --

18 DOCTOR LIPSKY: Well, that is, as you've  
19 heard everybody say about other things, a very  
20 complicated and controversial area. I think there are  
21 certain organisms that are certainly more virulent  
22 than others. Staph aureus is the major cause of  
23 serious infections in diabetic foot ulcers and our  
24 experience, and there is some support for this,  
25 suggests that if the patients, for example, go to

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 antaranerious colonization with staph aureus the y  
2 shed it on to their skin, it gets into their wound s  
3 and they often have recurrent staph infections an d  
4 using a topical agent like mupericin to eradicat e  
5 nasal staph aureus colonization stops the cycle o f  
6 recurrent infection.

7 So I think that there are particula r  
8 virulent organisms that may be worth looking a t  
9 controlling but that's not the issue that I understoo d  
10 was being addressed which was lowering the bioburden,  
11 reducing it from  $10^6$  down to  $10^3$  or so.

12 DOCTOR EAGLSTEIN: Finally, I just thank  
13 you for letting me make the comment and, as I said ,  
14 there are studies in other wounds that you hadn't bee n  
15 familiar with perhaps so thank you very much.

16 ACTING CHAIRMAN BERGFELD: Thank you ,  
17 Bill, and thank you for putting this on the table so  
18 it will be considered later.

19 We now have to look at three questions ,  
20 questions 3, 4 and 6 in that order, and it is m y  
21 intent to close the meeting at 5:30 at the latest. S o  
22 we will start with question 3 or topic 3, Entr y  
23 Criteria Indications and, as Doctor McGuire did in the  
24 past, I will read the question and then we'll open it  
25 for discussion.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           As discussed in the background material,  
2           the pathophysiological mechanisms underlying differen t  
3           types of chronic ulcers are not identical. In cases  
4           where the mechanism of action of a test agent is know n  
5           to target a parameter unique t o a certain wound type,  
6           subject with other types of chronic wounds woul d  
7           clearly be excluded from a clinical trial.

8           When the mechanism of action of a tes t  
9           agent is potentially relevant to all types of chronic  
10          ulcers, should efficacy be demonstrated separately fo r  
11          each major ulcer type or might a general evaluation i n  
12          chronic ulcers lead to a broad indication? How d o  
13          these considerations apply to the following types of  
14          products and then A through I think that's E which is  
15          antimicrobial agents, debriding agents, bio-engineere d  
16          skin substitutes, growth factors and others.

17          So I believe that we'll go back to th e  
18          first paragraph and restate it. As discussed in the  
19          background material, the pathophysiological mechanism s  
20          underlying different types of chronic ulcers are not  
21          identical. In cases where the mechanism of action of  
22          a test agent is known to targe t a parameter unique to  
23          a certain wound type, subject to other types o f  
24          chronic wounds would clearly be excluded from a  
25          clinical trial.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 I might ask if that is a unanimous  
2 decision of this panel, whether they would agree with  
3 that statement. I'd like a show of hands for  
4 affirmative. Yes. We move on then to the question.  
5 When the mechanism of action of a test agent is  
6 potentially relevant to all types of chronic ulcers,  
7 should efficacy be demonstrated separately for each  
8 major ulcer type? Let's answer that question. Any  
9 comment on that specific area? Doctor Lipsky and the  
10 Doctor Drake.

11 DOCTOR LIPSKY: Notwithstanding Doctor  
12 McGuire's reluctance to buy off on this yesterday, I  
13 still think that there is some evidence to support  
14 that. Diabetes mellitus does cause some immunologic  
15 and infectious perturbations. Having reviewed this  
16 topic for an NIH book called "Diabetes in America" and  
17 writing the chapter on diabetes and infection with one  
18 of our epidemiologists, we very rigorously surveyed  
19 the literature and there are at least a half dozen  
20 infections which clearly can be shown to be more - -  
21 have a higher incidence of patients with diabetes or  
22 a greater severity and I think, given the possibility  
23 of these immunologic perturbations or other problems  
24 that cause diabetic patients to have either more  
25 frequent or more serious infections, that they need to

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 be looked at somewhat differently from the infection  
2 control point of view at least.

3 ACTING CHAIRMAN BERGFELD: Doctor Drake.  
4 Thank you.

5 DOCTOR DRAKE: I think that as a  
6 pragmatist, as a bit of a pragmatist, I think it's  
7 important that we not make doing clinical research so  
8 cost prohibitive that new products can't come to the  
9 market because it's just impossible. At least I've  
10 heard an awful lot of common denominators here today.  
11 I mean basically all wounds need to be debrided  
12 irrespective of source. All wounds need microbial, at  
13 least some evidence that you take care of any  
14 infections. I think there's a lot of common ground on  
15 a lot of the wounds and to have to study everything in  
16 every group I think has a potential to make it cost  
17 prohibitive and, in fact, dampen the enthusiasm for  
18 industry to pursue some of these as well as dampen the  
19 enthusiasm for clinical investigators to try to do all  
20 this.

21 I think there's some very common ground  
22 that should be collectively lumped together and then  
23 once you prove the efficacy, as you start using it,  
24 clearly in phase four, maybe even in phase three but  
25 clearly by phase four, some of this stuff will start

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 sorting out. But on the front end, I think we need t o  
2 be a little b it pragmatic about what's rational.  
3 We're spending \$350 million sometimes to get a drug t o  
4 market , so I would like to see us be a bit of a  
5 clumper when it's possible.

6 ACTING CHAIRMAN BERGFELD: Doc tor Cooper.

7 DOCTOR COOPER: I would speak the opposit e  
8 of that. I think that increasingly we're learnin g  
9 that a wound is not a wound is not a wound and tha t  
10 separate wound types have varying characteristics and ,  
11 in particular, if you were to look at recombinan t  
12 cytokines and understanding gr owth factors, there are  
13 some wounds that heal primarily by deposition o f  
14 extracellular matrix and other ones that hea l  
15 primarily by epithelialization.

16 And so I would think that we've worke d  
17 long and hard, those of us in wound healing, to try t o  
18 detect the differences between these wounds so that we  
19 will understand them better, just as Doctor Lipsk y  
20 referred to the diabetic ulcer as another type o f  
21 wound. So I would speak for them being seen a s  
22 different.

23 ACTING CHAIRMAN BERGFELD: Yes.

24 DOCTOR MUSTOE: I think there's a middle  
25 ground which is it depends on the agent. If you'r e

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 talking about the debriding agent where your primary  
2 end point is not improved wound healing but just a  
3 debriding agent that doesn't make the wound worse, I  
4 think it probably could be applicable to all three  
5 wounds.

6 On the other hand, if your wound healing  
7 agent is you're making claims that it actually  
8 improves healing with the end point being a greater  
9 percentage of wounds healed, I think whether it's a  
10 cytokine or a cultured epithelial substitute, I think  
11 that the end point should in fact be specific for the  
12 major type of ulcer. So I think it really depends on  
13 what the claims of the product are.

14 ACTING CHAIRMAN BERGFELD: Yes, Ken .  
15 Doctor Hashimoto.

16 DOCTOR HASHIMOTO: I agree with Doctor  
17 Mustoe. There's some literature to indicate that .  
18 For example, in diabetic patients, some down -- o f  
19 cytokines production. In that case, supplementin g  
20 that cytokine may be very spec ifically beneficial for  
21 that type of ulcer.

22 ACTING CHAIRMAN BERGFELD: Doc tor Thomas.  
23 No comment. Doctor Miller, any comment abou t  
24 separating or clumping?

25 DOCTOR MILLER: I agree with what To m

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 said.

2 ACTING CHAIRMAN BERGFELD: There's general  
3 agreement over here.

4 DOCTOR MARGOLIS: I'm a splitter.

5 ACTING CHAIRMAN BERGFELD: You're a  
6 splitter. And you're splitting in which direction?

7 DOCTOR MARGOLIS: I would split along the  
8 way that Doctor -- said.

9 DOCTOR COHEN: Likewise.

10 ACTING CHAIRMAN BERGFELD: Likewise. So  
11 Doctor Drake, do you wish to comment? There is some  
12 commonality of what you said.

13 DOCTOR DRAKE: No. I think the group is  
14 right. I mean I totally agree with my colleague to my  
15 right here. I mean I have no disagreement at all with  
16 what you said. It's just what I was hearing was that  
17 we should separate them all and I don't think that's  
18 necessary all the time. I think there are cases, just  
19 as you outlined, when that's appropriate but if you're  
20 debriding something, I mean it's a whole debride. I  
21 don't think you have to run the cost of the study up  
22 by studying every type of wound. So I'm in total  
23 agreement.

24 ACTING CHAIRMAN BERGFELD: So I think that  
25 we've answered that general question. Going down to

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1       specifics then, how do these considerations apply to  
2       the following types of products? There was mention of  
3       the debriding agents which may be common to all of the  
4       ulcer sites and the first one here is A) antimicrobial  
5       agents. Would they be specific to all types or would  
6       they be individualized to a specific type of ulcer?  
7       Generalized. The comment is they'll be generalized as  
8       we have done the debriding agents in general. Any  
9       other comment about that? It should be generalized  
10      microbial approach.

11                   DOCTOR ROSENBERG: Are there kinds of  
12      ulcers that have their own special flora?

13                   ACTING CHAIRMAN BERGFELD: Doctor Lipsky.

14                   DOCTOR LIPSKY: They're more similar than  
15      they are different, I think.

16                   ACTING CHAIRMAN BERGFELD: So the ulcer's  
17      microflora is similar no matter what the source of the  
18      ulcer or the etiological agent?

19                   DOCTOR LIPSKY: There are some  
20      differences. Certainly with diabetes, staph aureus  
21      and candid albicans are more commonly isolated and  
22      organisms of relatively low virulence, cornea  
23      bacterium species, coagnegative staph and so on are  
24      more apt to be pathogens whereas you might dismiss  
25      them in an otherwise healthy or at least non-diabetic

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 individual. But I would lean toward the side of the  
2 microbiology and response to infection being mor e  
3 similar than different when it comes to responding to  
4 an antimicrobial agent.

5 ACTING CHAIRMAN BERGFELD: And I se e  
6 general consensus. Ms. Cohen.

7 DOCTOR COHEN: Well, I'd be concerned tha t  
8 the claims would be made in the inserts or in th e  
9 advertising that it can do all these things and, i f  
10 they say it can do all these things, then it has to b e  
11 substantiated.

12 ACTING CHAIRMAN BERGFELD: I think there' s  
13 general agreement that you have to substantiate your  
14 marketing claims.

15 We've covered the debriding agents. Goin g  
16 on to C, the bio-engineered skin substitutes. Would  
17 there be a difference in the ulcer types or woul d  
18 these guidelines be generically applied to all these  
19 ulcer types? There's a difference, Doctor Thoma s  
20 says. Do you want to expand on that at all?

21 DOCTOR THOMAS: No. If everyb ody agrees,  
22 we can go on to the next one.

23 ACTING CHAIRMAN BERGFELD: All right .  
24 Does everyone agree that there's a difference in the  
25 ulcer sites as they are associ ated with the treatment

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 of bio-engineered skin substitutes? Doctor Lipsky ,  
2 are you shaking your head?

3 DOCTOR LIPSKY: I just don't know.

4 ACTING CHAIRMAN BERGFELD: You don't know .  
5 Well, there may be a difference then so they perhaps  
6 should be studied differently or individually. An y  
7 other comment? Doctor Cooper?

8 DOCTOR COOPER: No. I agree.

9 ACTING CHAIRMAN BERGFELD: The y should be  
10 separated in the study of that particular product. D ,  
11 growth factors. A difference. Looks like genera l  
12 consensus is difference. Doctor Rosenberg.

13 DOCTOR ROSENBERG: The growth factor' s  
14 story has been a disappointing one. I mean th e  
15 epidermal growth factor data t hat *New England Journal*  
16 publications. Unless I'm wrong, my belief is it' s  
17 been a disappointment and the thing about the growth  
18 factor is these are chemical messages. We saw th e  
19 slide that was put up yesterday showing ho w  
20 complicated all these messages were and these ar e  
21 just, they're not even words. They're not messages.  
22 They're letters. They're symbols. You can write a  
23 short story without the letter B and people have done  
24 those kinds of exercises. You put more Bs in. An d  
25 the same message shows up or the same group of letter s

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 shows up at different times in different parts of the  
2 story and I think making things happen or keep the m  
3 from happening by pulling out two letters is naiv e  
4 unless it can be shown to really work.

5 I understand that the hemopoietic growth  
6 factors really work in certain instances, but if i t  
7 could be shown that some kind of non-healing skin was  
8 non-healing because of a failure, that that particula r  
9 keyboard lacked the letter B and that putting it i n  
10 would make the story flow better, then that' s  
11 terrific. But until we see that, I think a hig h  
12 standard ought to be required of those who would tell  
13 us that by throwing a couple of letters into th e  
14 machine you're going to get the works of Shakespeare  
15 come out.

16 ACTING CHAIRMAN BERGFELD: But it' s  
17 already been suggested that diabetic ulcer may b e  
18 cytokine deficient, and specifically in that type of  
19 ulcer this might be helpful.

20 DOCTOR ROSENBERG: If that were so, then  
21 it would -- precisely.

22 ACTING CHAIRMAN BERGFELD: Yes, Docto r  
23 Weiss.

24 DOCTOR WEISS: I was just going to clarif y  
25 that hemopoietic growth factors, which we've had a lot

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 of experience at our center in reviewing and  
2 approving, they do work but we have asked that and  
3 we've asked the Biologics Response Modifiers Committee  
4 issues regarding standards for these things. We've  
5 asked that our manufacturers demonstrate that they  
6 work in, for instance, bone marrow transplant as  
7 opposed to just multi-cycle chemotherapy. They're  
8 different settings and we've gotten the message very  
9 clearly that we can't generalize. Just because it  
10 works in a mild ablative setting doesn't necessarily  
11 mean it'll work in a less intensive chemotherapy  
12 setting. I think that's the kind of question we're  
13 asking here. If something works in a diabetic ulcer,  
14 it doesn't necessarily mean that it would work in a  
15 pressure ulcer and that kind of thing.

16 ACTING CHAIRMAN BERGFELD: Well, I think  
17 that the unanimous decision was that they had to be  
18 studied, the different ulcer types, individually.

19 Doctor Thomas.

20 DOCTOR THOMAS: And just one thing to  
21 point is that we seem to have gone through this list  
22 and said that each of these are different in the study  
23 of different wounds with the exception of debridement.

24 ACTING CHAIRMAN BERGFELD: And maybe wound  
25 cleansing. We didn't cover that.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DOCTOR THOMAS: We didn't cover that but  
2 we can speak to that, too. And I think that if you'r e  
3 talking about surgical debridement, then it probably  
4 should be the same but if you're talking abou t  
5 chemical agent debridement, there may be differences  
6 among the wounds.

7 ACTING CHAIRMAN BERGFELD: So you'd like  
8 reconsideration of the debriding techniques, whether  
9 they be chemical or physical or microbiological.

10 DOCTOR THOMAS: I think that there ar e  
11 reasons to think that there may be some difference s  
12 and just pointing out the fact that we've now gon e  
13 through this whole list and said they ought to b e  
14 studied differently with the exception of one thin g  
15 and we don't really have a lot of data to accept that  
16 one thing.

17 ACTING CHAIRMAN BERGFELD: Any othe r  
18 comment on growth factors or a ny of the other factors  
19 here? Joel.

20 DOCTOR MINDEL: Is there sufficien t  
21 economic incentive for all thr ee kinds of ulcers that  
22 a manufacturer would be willing to study all thre e  
23 separately or are you creating therapeutic orphans by  
24 splitting?

25 ACTING CHAIRMAN BERGFELD: Doc tor Thomas.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DOCTOR THOMAS: I agree and th at's a very  
2 valid point. I just want to f lip it around the other  
3 way and say that the other way of saying this is that  
4 if you do a study that shows that it works i n  
5 neuropathic diabetic ulcers, then what I think th e  
6 agency is asking is then can y ou make a claim that it  
7 will work in the other two. And I think that's what  
8 we're saying. I agree with you. There are problems  
9 about splitting this. It makes sample size difficult .  
10 It makes getting patients difficult, and I hate th e  
11 idea, but there are physiological reasons to thin k  
12 that they're different enough so that we couldn't do  
13 the flip side which is to say okay, you've proven tha t  
14 it works in this so now you ca n use it in all wounds.  
15 I don't think that's the hurdle we want to make.

16 ACTING CHAIRMAN BERGFELD: Doctor Drake.

17 DOCTOR DRAKE: Question, Doctor Thomas .  
18 Are you saying that if, say, a product comes forward  
19 that you think, might have reason to believe woul d  
20 work in a pressure ulcer which is your area, you'r e  
21 saying that either they should -- they say they must  
22 study all the ulcers to determine that because let's  
23 say if they limit it to pressure ulcers and it works  
24 and once it's approved, the st andard of practice will  
25 be that people will try it in other forms of ulcers.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 So I guess I'm a little confused. Do you think i f  
2 anybody wants to do anything in wound healing, the y  
3 have to define the type of ulcer that they'r e  
4 addressing in order to get it approved? Could yo u  
5 clarify for me a little bit.

6 DOCTOR THOMAS: I'm coming in a backwards  
7 way from this. What I'm saying is that if you do a  
8 study that demonstrates that it works in pressur e  
9 ulcers, then you can not make a claim that it's going  
10 to be equally effective in diabetic ulcers or venous  
11 stasis ulcers.

12 DOCTOR DRAKE: I understand th at. But if  
13 somebody came forward to the agency then and said we  
14 want to study product X for ulcers, you would b e  
15 opposed to that. You would say that we must stud y  
16 product X for pressure ulcers.

17 DOCTOR THOMAS: No. Whatever stud y  
18 anybody wants to do and whatever wound they think it' s  
19 going to work in, they're going to make a claim that  
20 it works in that wound.

21 DOCTOR DRAKE: I.e., a specific type o f  
22 ulcer.

23 DOCTOR THOMAS: Yes.

24 DOCTOR DRAKE: Okay.

25 DOCTOR THOMAS: In other words, if you sa y

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 this works for all wounds and you only have studie d  
2 one kind of wound, you really don't know that it work s  
3 in the other wounds and we have been hearing for the  
4 last two days that there may be substantia l  
5 differences in the treatment of these wounds. Also,  
6 you've got differences in the control arm. You've go t  
7 differences in compression. You've got differences i n  
8 offloading. You've got differences, differences ,  
9 differences, differences and I think it would b e  
10 inappropriate for somebody to say, well, now, we'v e  
11 done a really neat study in venous stasis ulcers and  
12 so you should use this on scalp lacerations.

13 ACTING CHAIRMAN BERGFELD: Doc tor Mustoe,  
14 you have a comment on this.

15 DOCTOR MUSTOE: I would agree with Doctor  
16 Thomas and just again, if the claim is actually t o  
17 improve wound healing with the end point bein g  
18 complete wound closure or completely closed wound ,  
19 you've got to study each ulcer type and I think that  
20 is the consensus of the board. I think if you ar e  
21 this panel, I think if you are talking about an agent  
22 that has another end point, it may not be necessary t o  
23 study all three ulcers independently.

24 ACTING CHAIRMAN BERGFELD: Any othe r  
25 comments regarding this question. There is an E )

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Other. Are there any other combinations that we might  
2 consider? No. Then moving on to the second part of  
3 this question which deals with the covariates and  
4 certainly the statisticians, if you'll help us with  
5 this one. The paragraph is long but it states, "The  
6 following covariates have an impact on wound healing. "  
7 And these are listed. Surface area, depth and  
8 chronicity of ulcers, presence of arterial and venous  
9 insufficiency, anatomical sites involved, age of the  
10 subjects, condition of the subjects, microflora  
11 balance of wounds.

12 "In clinical trials, these covariate s  
13 potentially can be used as entry criteria and  
14 ultimately to define the specific drug/devic e  
15 indication as variables for stratification and/o r  
16 covariates for assessing outcome. Please describe th e  
17 impact of these covariates on the measurement o f  
18 safety and efficacy of wound healing studies and  
19 discuss how they should be handled in clinica l  
20 trials."

21 So you deal with the age of the patient,  
22 the conditions of the patient, the ulcer itself b y  
23 size and depth and chronicity and etiology and  
24 specifically noted here arterial and venou s  
25 insufficiency but there could be added others and then

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 microfloral. Yes.

2 DOCTOR LAVIN: Probably my sense on this  
3 is that I would add one to that which would be th e  
4 invest igative site and if I were doing th e  
5 stratification, I would recommend that clearly al l  
6 studies be stratified by the investigator site. I  
7 think the need to stratify for all of those factors a t  
8 the same time would be a prodigious task, not really  
9 wise or recommended, but they are in the right spirit  
10 of what should be collected that should be included i n  
11 an analysis of outcome and so it would be in logistic  
12 regression that these would be included as covariates  
13 or some type of a proportional hazards model and time  
14 to events, so these are wise to include but not fo r  
15 stratification necessarily.

16 ACTING CHAIRMAN BERGFELD: Yes, Docto r  
17 Margolis.

18 DOCTOR MARGOLIS: I would argue that thes e  
19 are certainly important. Cert ainly the spirit of the  
20 question is important in terms of your analysis but I  
21 would argue that these are actually different fo r  
22 different wounds. There are s tudies that have looked  
23 at these for each of the different wound types an d  
24 they aren't always the same. I think it's a  
25 misconception to think that yo u should always look at

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the same things for all the wounds. And you can pick  
2 ones out that don't fit venous leg ulcers from this  
3 group and you can pick ones out that don't necessarily  
4 fit pressure ulcers from this group.

5 ACTING CHAIRMAN BERGFELD: So your  
6 comments relate to separating the ulcer types and then  
7 the covariates might differ slightly one from another.

8 DOCTOR MARGOLIS: Yes.

9 ACTING CHAIRMAN BERGFELD: Doctor Cooper.

10 DOCTOR COOPER: I would just like to  
11 concur with that because, in particular, in the venous  
12 ulcer, it really has become evident that you need to  
13 stratify from the small ulcers up and the large ulcers  
14 down to really get meaningful results.

15 ACTING CHAIRMAN BERGFELD: Doctor Miller.  
16 Doctor Clint Miller.

17 DOCTOR MILLER: I would add two caveats to  
18 the observations just made. The first of these is  
19 that you should perhaps review this list and stratify  
20 on those variables that you anticipate are not going  
21 to change throughout the duration of the trial. Those  
22 that you think are time dependent then obviously  
23 should be used as covariates.

24 I also would hasten to add that those  
25 covariates should be considered concomitantly, not

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 singly or one at a time, in order that you might  
2 assess their added effects but also their interaction  
3 and those models should include those interactions.

4 And the final thing is I encourage the  
5 analysis and the designs to again return to this  
6 effort to develop a multi-dimensional outcome space so  
7 that you can make trade-offs in various outcomes,  
8 dependent upon the need of the management of the  
9 individual patient.

10 ACTING CHAIRMAN BERGFELD: Any other  
11 questions you'd like us to address, FD A  
12 representatives? All of you, six of you. Thank you.

13 DOCTOR WEISS: You've got a good sense.

14 ACTING CHAIRMAN BERGFELD: We've got a  
15 good sense of that one. Good. Thank you very much  
16 for all of your comments then. We'll move on to topic  
17 four, wound assessment, and we'll take the -- this is  
18 a four part question. We'll take just the opening and  
19 then one question at a time.

20 "Standardized methods for wound assessment  
21 are critical to the design of clinical trials and the  
22 terms of defining the study population, monitoring  
23 safety, and evaluating efficacy." The first question  
24 "What diagnostic technique should be performed in  
25 order to confirm the clinical diagnosis of each type

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 of ulcer? Should the evaluation include biopsy? If  
2 so, by what technique?"

3 Anyone like to respond to that first?

4 DOCTOR COOPER: Yes.

5 ACTING CHAIRMAN BERGFELD: Yes, Doctor  
6 Cooper.

7 DOCTOR COOPER: In clinical trials I've  
8 already expressed by views, but I'll reiterate them.  
9 In the venous ulcer, I think it should be tissue  
10 biopsy for quantitative bacteriology and in the  
11 pressure ulcer also.

12 ACTING CHAIRMAN BERGFELD: Doctor Mustoe.

13 DOCTOR MUSTOE: Yes. I think that to  
14 make the diagnosis, I think biopsies are not  
15 necessary. I think in terms of quantitative  
16 bacteriology I would go to Doctor Lipsky's. I  
17 recognize that -- I just don't think there's a  
18 consensus into the -- I think the quantitative  
19 bacteriology has value. I just think the -- I'd like  
20 to think that there are alternative ways to get a  
21 that answer than biopsies.

22 ACTING CHAIRMAN BERGFELD: Doctor Lipsky,  
23 do you want to respond?

24 DOCTOR LIPSKY: Well, to somewhat  
25 reiterate statements made previously, I guess the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 question I would ask is what you do with tha t  
2 quantitative bacteriology information. If you someho w  
3 stratify patients, the question would be on wha t  
4 basis? So if you're not using that information or if  
5 you're using that information without adequate studie s  
6 to support your use of it, the n I don't see the value  
7 to it.

8 I also have concerns about biopsyin g  
9 diabetic foot ulcers in particular with the problems  
10 with vascular supply and wound healing issues tha t  
11 come up with those patients. We're reluctant t o  
12 biopsy those wounds, especially distal toe lesions ,  
13 for example, where the wounds might be quite small .  
14 So for all of those reasons, I don't see the need for  
15 this but I would love to see a study of it looking at  
16 whether or not it has any value.

17 ACTING CHAIRMAN BERGFELD: I'd like t o  
18 summarize what we have spoken about the earlier part  
19 of the day and that is to say the only questionabl e  
20 ulcer for biopsy was that of t he venous stasis ulcer.  
21 The diabetic ulcer and the dec ubitus ulcer, I believe  
22 we came to some resolution in many conversations that  
23 that did not need to be biopsi ed. Perhaps culture if  
24 it looked infect ed, but that was the only time.

25 Doctor Rosenberg.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DOCTOR ROSENBERG: My understanding of th e  
2 question was should you have a biopsy to define th e  
3 nature of the ulcer and I would point out that wit h  
4 yourself and Doctor Hashimoto at the table, two highly  
5 regarded histopathologists, I would yield to you r  
6 judgement and my guess would be not, but I'd like to  
7 hear both of you say yes or no.

8 ACTING CHAIRMAN BERGFELD: I would say no .  
9 I hate them when they come.

10 DOCTOR HASHIMOTO: Well, I think as a --  
11 pathologist I can not be 100 percent sure but at leas t  
12 you see some parameter like hemo -- stasis ulcer, --  
13 ulcer. You have a thickened basement membrane -- so  
14 some criteria there. I don't know. It's not worked  
15 out. It's not extensively studied. No one took 100  
16 percent interest in this area, so it's unexplored  
17 field. Probably if someone seriously tackled dow n  
18 this problem, come up with some significant data.

19 ACTING CHAIRMAN BERGFELD: What you've e  
20 heard then is that perhaps a biopsy is not needed ,  
21 that the clinical diagnosis may be adequate in all the  
22 parameters used to make that, that a biopsy i s  
23 questionable for determining the bacterial flora ,  
24 specifically in the venous ulcer, and that is eve n  
25 debatable whether that is necessary and you've heard

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 from Doctor Hashimoto and I will support his statement  
2 that the histopathology of ulcers have not been  
3 established as a standard so it's all in  
4 interpretation and sometimes not too helpful. I think  
5 that perhaps we've answered that question then.

6 If we don't mind, we'll move on to  
7 question two under the same topic of wound assessment  
8 and this question reads, "There are multiple methods  
9 of measuring ulcers and documenting the findings .  
10 Examples are measurements of maximum dimensions ,  
11 tracings of the perimeter of the ulcer and planimetry ,  
12 probing to establish depth, preparations of molds ,  
13 photography of the ulcers. These methods vary in  
14 precision and invasiveness. Please discuss the merits  
15 and disadvantages of these and other methods for  
16 measuring the surface area and depth of the chronic  
17 cutaneous ulcers. Do you recommend that photography  
18 be used for documentation?"

19 Doctor Cooper.

20 DOCTOR COOPER: I think once again you  
21 have to look at the major mechanisms by which these  
22 various types of wounds are healing. Obviously, a  
23 venous ulcer is not a wound of depth. I mean it's of  
24 minimal depth and so things like alginate molds would  
25 be inappropriate. But I think that increasingly over

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 time there's been greater clarification of th e  
2 clustering of measurement tools that are reall y  
3 adequate of varying levels of rigor that should b e  
4 applied to the specific wound types.

5 And the final question is about t  
6 photography and I think photog raphy is essential, not  
7 necessarily for some of the other reasons we spok e  
8 about throughout the day but I think once again a  
9 picture is worth a thousand words and in good clinica l  
10 settings pictures are taken with extreme skill an d  
11 precision and over time you really have data of th e  
12 evolution of that wound and that's very importan t  
13 information which up to this time we haven't had.

14 ACTING CHAIRMAN BERGFELD: Yes, Docto r  
15 Miller.

16 DOCTOR MILLER: The issue with th e  
17 neuropathic ulcers, I think it's come out repeatedly  
18 that there's really a paucity of studies that are of  
19 any value and I think we saw yesterday with th e  
20 multiple anatomic sites of those ulcerations and how  
21 difficult it was to determine which lesions wer e  
22 healing and at what rate they were healing and wha t  
23 was the final result and which ones did actually heal .

24 And I think that at the outset the studie s  
25 have to be set up, looking specifically at th e

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 neuropathic ulcers, that there 's a homogeneity to the  
2 ulcers, that these are going to be metatarsal head  
3 ulcers that are studied, heel ulcers that are studied ,  
4 toe ulcers that are studied and then you'd have to  
5 talk about dorsal toe, you'd have to talk about toe  
6 pads and I think that because of the difficulty in  
7 diagnosing neuropathic ulcers and the lack of  
8 unanimity in the diagnosis and the lack of  
9 understanding among physicians and among others that  
10 photography is really necessary and I think that there  
11 should be a location shot and then a close up of each  
12 of the ulcers in the study and then, in addition, you  
13 can do the measurements as you go through it . But you  
14 should have a location and a close-up. If you just  
15 take a close-up of an ulcer, you can't really see  
16 exactly where it is on the foot and I would like to  
17 know, where is it on the metatarsal head, which  
18 metatarsal head is it, and then what did this ulcer  
19 look like and then show me what it looks like when  
20 it's healed.

21 But I think until we get a homogeneity of  
22 ulcers in these studies, we're not going to be able to  
23 come to any conclusions with the neuropathic ulcers.  
24 We discussed for hours yesterday and at the end I  
25 really wasn't sure what had healed.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1                   ACTING CHAIRMAN BERGFELD:    Yes, Docto r  
2                   Lipsky.

3                   DOCTOR LIPSKY:   Two comments.   The first  
4                   is on photography.   As you all    know, we're developing  
5                   digital photography.   It's get   ting better and cheaper  
6                   and in the future we'll easily be able to digitiz e  
7                   these wounds and give you certainly dimensions an d  
8                   probably with stereoscopic cameras even depth, so   I  
9                   think we ought to be moving in   that direction, and th e  
10                  FDA is asking us about not only what's going on no w  
11                  but what will happen in the future.

12                  The second issue has to do with probin g  
13                  the wound.   The question was phrased, "probing th e  
14                  wound to determine its depth as a measurement" but I  
15                  would say in the diabetic wound it has to be probe d  
16                  for two other reasons.   One is the slides you sa w  
17                  yesterday where wounds that looked like they wer e  
18                  shallow in fact could easily be demonstrated with a  
19                  little bit of pressure to go t hrough the foot and you  
20                  need to know that.

21                  Secondly, there's now good data that the  
22                  probe to bone test that has been   worked on in a numbe r  
23                  of centers, particularly the New England Deaconess, i s  
24                  probably as accurate as \$1,000 MRI in terms o f  
25                  determining whether or not the re's osteomyelitis.   So

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 all diabetic wounds should be probed for those two  
2 reasons.

3 ACTING CHAIRMAN BERGFELD: Doctor Miller.

4 DOCTOR MILLER: I would like to speak in  
5 support of Doctor Lipsky's comment. Digital cameras  
6 now are very, very, very good and they're even doing  
7 a good job at stereoscopy and so I'm certain that  
8 that'll become an important part of documentation in  
9 the medical record. The word, by the way, digital is  
10 very interesting because it means that information is  
11 objectively available to the analyst and to the  
12 clinician and that's going to be a much improved  
13 documentation over just the typical light camera.

14 The other thing I'd like to say is that  
15 almost each of these proposed measurements for ulcers  
16 can have arguments for them and against them. For  
17 example, earlier Doctor Thomas was concerned about the  
18 linearity of the growth of the skin, etcetera, around  
19 a pressure sore. The fact that it was nonlinear. I  
20 think you could make arguments for all those and I  
21 think that the FDA when they enumerate all these  
22 alternative measurements ought to consider just  
23 looking in the literature and find out what the pluses  
24 and what the minuses are and what the corrections,  
25 appropriate corrections that have been suggested for

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 those different kinds of measures. That wouldn't take  
2 very long to do that and it'd be very helpful in  
3 guiding the choice of outcomes or end points.

4 ACTING CHAIRMAN BERGFELD: Doctor Drake.

5 DOCTOR DRAKE: This is just a suggestion  
6 but I know at Mass General in some of the labs there,  
7 there's so much going on in imagining and looking at  
8 signalling. There's probably some new methodologies  
9 out there that could be potentially extraordinarily  
10 helpful in giving you quantifiable measures of wound  
11 depth, wound parameters. I mean it can be done  
12 quickly just with simple imaging. There are several  
13 labs up there including the Wellman Labs from which I  
14 come that are doing all kinds of -- work, photocoustic  
15 work using a marker dye and capturing that  
16 information. It might be worth thinking about an RFP  
17 on just how best to do this because this is such a  
18 huge burden to the patients and if there's a simple  
19 way that one could standardize the measurement of it  
20 by a portable instrumentation, then that might be  
21 really worth particularly the device industry looking  
22 into. You might even want to issue an RFP. I know  
23 there's an awful lot percolating around out there on  
24 it now and it might be worth pursuing.

25 ACTING CHAIRMAN BERGFELD: Thank you. I

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 think the group has answered the questions. I think  
2 there's no doubt that some type of documentation o f  
3 the size of the ulceration and the depth as well as a t  
4 beginning, at the end of therapy needs to be done .  
5 The probing also has had unanimous support, especiall y  
6 the diabetic ulcer and perhaps the pressure ulce r  
7 specifically. The mention of new technology availabl e  
8 and perhaps seeking a method to obtain that ne w  
9 information might be helpful. Have we forgotte n  
10 anything?

11 DOCTOR MILLER: Let's not forget th e  
12 journey.

13 ACTING CHAIRMAN BERGFELD: The journey .  
14 Which would mean serial whatever is done to evaluate  
15 the ulcer site and size and depth. All right. Then  
16 moving on to question three under wound assessment .  
17 "At this time, the agency is not aware of any full y  
18 quantitative means of assessing the amount of eschar  
19 present in an ulcer that has been debrided. Pleas e  
20 discuss how to best evaluate the adequacy o f  
21 debridement.

22 Doctor Mustoe, maybe you would start.

23 DOCTOR MUSTOE: Well, I would -- m y  
24 impression was -- would have b een, and this is not an  
25 area that I've studied, that photographically tha t

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 certainly a wound that is pink or red, the percentage  
2 of wound that's pink or red has been adequately  
3 debrided but obviously in something that's black it is  
4 obviously necrotic and hasn't been debrided but I  
5 gather Doctor Margolis has said that in fact  
6 photography was not terribly at evaluating  
7 debridement. I think debridement to me is one of the  
8 most subjective areas around. I just I think it's  
9 going to be hard to define adequacy. I really think  
10 it's a tough issue.

11 ACTING CHAIRMAN BERGFELD: Doctor Drake,  
12 then Doctor Fred Miller.

13 DOCTOR DRAKE: Now, this is an area where  
14 there is a new methodology that I'm quite familiar  
15 with for measuring eschar if you've removed it  
16 effectively or not. Doctor Norm Nishioka who's at the  
17 Wellman Laboratories at Mass General has really led  
18 the research on it. There's lots of publications  
19 around. It's involving burn wounds. And they started  
20 out using like indocyanine green and by injecting it  
21 using rapid signalling back and forth to smart lasers,  
22 you could manage the cutting tool where if you got a  
23 signal, it didn't cut the tissue. It only cut dead  
24 tissue and they're specific down to 15 microns. And  
25 they've even moved that work further along and so that

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 might really be worth exploring. He's a  
2 gastroenterologist but he's a photophysicist and  
3 they're working intensively in this area.

4 ACTING CHAIRMAN BERGFELD: Doctor Fred  
5 Miller.

6 DOCTOR FRED MILLER: As Tom said, Dave  
7 taught us this morning that the photography isn't that  
8 helpful or can misrepresent a wound. I think a lot of  
9 it is subjective. You know, you debride until you  
10 get to what is viable tissue. What is viable tissue?  
11 It has a different appearance. It is pink. There's  
12 no eschar there. There's not any necrotic material.  
13 But I don't know how to quantify it.

14 ACTING CHAIRMAN BERGFELD: Thank you .  
15 Tom.

16 DOCTOR MUSTOE: Yes. I just think the dye  
17 studies are intriguing. I just don't know if they've  
18 been studied but one area that is used in plastic  
19 surgery commonly which is clearly well known is  
20 flouricenine injections which are pretty safe .  
21 Unfortunately, they're not 100 percent safe. There is  
22 rare anaphylaxis and that's the problem. But  
23 flouricenine dye can with UV light very effectively  
24 show what's profused. But again, I can envision if a  
25 wound is actively bleeding, you know, you could have

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 flouricenine spilling out and staining other tissue,  
2 so I just think that when you take on new technology  
3 it's potentially very promising but I think you've e  
4 first got to do a study to validate and that's a tough h  
5 one.

6 ACTING CHAIRMAN BERGFELD: Docto r  
7 Harkless, Doctor Margolis, anything? Nothing?

8 DOCTOR HARKLESS: I would concur wit h  
9 Doctor Miller, what he said overall.

10 ACTING CHAIRMAN BERGFELD: So it look s  
11 like mechanical debridement wi th visual inspection is  
12 the recommendation and then a look at some of the new  
13 technology for assessing the eschar depth and viable  
14 tissue. Doctor Drake?

15 DOCTOR DRAKE: In fact, this technolog y  
16 has been validated. They've worked very carefull y  
17 with the surgical team from the Shriner's Burn. I  
18 mean this has been validated. It's well published .  
19 It's been well funded by the government. It's about  
20 seven years into the work and they're over clinica l  
21 trials now and I think it's really a new technolog y  
22 that has been well validated and it might be o f  
23 interest to all of you who work in this arena.

24 ACTING CHAIRMAN BERGFELD: Thank you.

25 DOCTOR HARKLESS: Can I comment?

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1                   ACTING CHAIRMAN BERGFELD:       Docto r  
2 Harkless.

3                   DOCTOR HARKLESS:     I've been teachin g  
4 residents what's normal and abnormal, hope that they  
5 operate on normal feet in terms of bunion activities  
6 and elective foot surgery so I tell    them if it doesn' t  
7 look like normal tissue, then it's abnormal and i t  
8 needs to be debrided and I don't think it takes    a  
9 rocket scientist to figure that out.

10                  ACTING CHAIRMAN BERGFELD:    Okay. Than k  
11 you. I see no other comment. We'll go on to par t  
12 four.

13                  "How should wound infection be    evaluated,  
14 monitored? Is quantitative cu lture after debridement  
15 the most acceptable means of demonstrating bacterial  
16 balance?"

17                  Doctor Lipsky, this is in your area o f  
18 expertise, if you don't mind answering first.

19                  DOCTOR LIPSKY: Well, we've discussed thi s  
20 issue a couple of times already. I think you star t  
21 with when you evaluate it, is infection present o r  
22 not, and I've already stated my very    simplistic way o f  
23 trying to make that assessment. In terms o f  
24 monitoring, if you're treating with an antimicrobial  
25 for clinically infected lesion, I think it' s

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 reasonable to consider getting a culture and follow up  
2 as evidence of microbial cure of the infection.

3 The reality is that if signs and symptoms  
4 of the infection disappear, then you will still get  
5 positive cultures. So I have a hard time knowing what  
6 to make of the culture results in a wound that is  
7 either healed or healing so the clinical outcome  
8 trumps the microbiological outcome in my view.

9 Quantitative cultures I've spoken to in  
10 the concept of bacterial balances is one that I don't  
11 think most infectious disease people think about. I  
12 think we know that there are places that bacteria are  
13 normally present. We know that there are places where  
14 certain bacteria shouldn't be, even if other bacteria  
15 are, and we know that there are places like your blood  
16 stream that shouldn't have any bacteria. But what is  
17 a balance in a colonized or contaminated or infected  
18 wound is very difficult to define.

19 I think we've spoken to the issue of  
20 choosing a number such as  $10^5$ , and where there is data  
21 to support that and where there isn't, at least in my  
22 view, sufficient data to use that number. So as a  
23 rule, I would like to see more studies looking  
24 specifically at the issue as to whether quantitative  
25 microbiology is of value in assessing the presence or

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 response of a wound, presence of infection or response  
2 of a wound to antimicrobial therapy. But at this  
3 point, I don't think there's sufficient evidence to  
4 demonstrate its usefulness to include it in routine  
5 clinical trials.

6 ACTING CHAIRMAN BERGFELD: I have to ask  
7 you a question. When you ended with that statement,  
8 realizing that all of the information that was put  
9 forth and discussed in the last day, actually two  
10 days, was for infection control of the wound. Now,  
11 unless you in some way make an assessment of that up  
12 front, how does that fit into the whole sense of  
13 what's happening with this ulcer as it supposedly  
14 heals or doesn't heal?

15 DOCTOR LIPSKY: Right. That was the first  
16 question that I asked yesterday in the presentation is  
17 what does infection control mean to the sponsor of the  
18 study who did the study and I got an answer that I  
19 don't really find very helpful to me. I think that  
20 one has to assess at the beginning whether or not you  
21 think infection is present and, if it is present, one  
22 has to use standard methods for determining whether  
23 the infection is responding to the antimicrobial  
24 effect of the product that you're using and that's  
25 pretty well worked out for skin and soft tissue

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 infections.

2 If it's an uninfected wound, it's mor e  
3 debatable as to whether or not one has to reduc e  
4 bioburden or knock down numbers or get rid of specifi c  
5 organisms. My own feeling at this point is tha t  
6 there's insufficient data to support the need to d o  
7 that so if I were treating a wound that I didn't thin k  
8 was clinically infected, I wouldn't normally culture  
9 that wound. I would treat it in the ways we've talke d  
10 about. Should the wound devel op signs or symptoms of  
11 an infection, I would then culture it, start th e  
12 patient on empiric therapy and modify that therap y  
13 based upon the results of the cultures an d  
14 sensitivities and the clinical response to the empiri c  
15 therapy that I'd started.

16 ACTING CHAIRMAN BERGFELD: Thank you.

17 Doctor Cooper, would you mind responding  
18 to this or endorsing these remarks?

19 DOCTOR COOPER: I disagree with them.

20 ACTING CHAIRMAN BERGFELD: Wou ld you mind  
21 stating them then for posterity.

22 DOCTOR COOPER: -- quantitativ e  
23 bacteriology at this time and I can not cite them all  
24 but when I find them I will send them to Doctor Lipsk y  
25 regarding the chronic wound. Has been established in

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 multiple studies which have shown that the wound that  
2 has bacterial burden greater than 10<sup>5</sup>, or strep does  
3 not heal. And there are specific organisms that come  
4 up that are the ones that are the problematic  
5 organisms in chronic wounds and swab cultures are 22  
6 to 29 percent correlated with tissue biopsy. So I  
7 wouldn't do a swab culture again in my life.

8 So I'm interested these wounds have been  
9 stuck, they don't show inflammatory responses because  
10 they've had chronic inflammation because they're  
11 trying to heal. They just keep pouring out  
12 inflammatory mediators, etcetera, and they -- I mean  
13 I certainly agree that I think there should be more  
14 studies, but I think to disregard over 30 years of  
15 work by Robson, Kruzek, Eggars and others is -- it  
16 wasn't just all on burns.

17 ACTING CHAIRMAN BERGFELD: Any other  
18 comments? Yes, Doctor Harkless.

19 DOCTOR HARKLESS: I would say that my  
20 experience at our institution in the Department of  
21 Orthopedics is similar to Doctor Lipsky's comments and  
22 we ran a -- foot course for 12 years and consistently  
23 get about 350 people and I've lectured extensively in  
24 my career and I would say almost always when this  
25 issue comes up it supports what Doctor Lipsky is

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 saying in terms of your clinical impression and I  
2 think that's what Doctor Miller clearly state d  
3 yesterday.

4 DOCTOR COOPER: But you're all talkin g  
5 about diabetic wounds. That's only one wound type.

6 DOCTOR HARKLESS: That's fine. That' s  
7 basically what we were talking about.

8 DOCTOR LIPSKY: We said that.

9 ACTING CHAIRMAN BERGFELD: Doc tor Mindel.

10 DOCTOR HARKLESS: That's what the stud y  
11 was about yesterday.

12 DOCTOR MINDEL: If quantitativ e  
13 microbiology is performed at the beginning of th e  
14 study and then it's two weeks into the study, how do  
15 your initial findings correlate then with th e  
16 subsequent microbiological contamination of the --

17 DOCTOR COOPER: In clinical trials wha t  
18 we're trying to get at is homogeneous subgroups an d  
19 one of the variables that leads us to be able to d o  
20 that is to be able to say that we can -- at th e  
21 entrance to the trial there is no evidence of tha t  
22 amount of bacteria or of strep. If they have that ,  
23 they can not go into the trial until they have a  
24 biopsy that is less than that and they are treat e d  
25 prior to that because we know that infection requires

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 entrance and growth into the tissue and so they ar e  
2 treated topically with antimicrobials and then the y  
3 have a wash out period and then they go into th e  
4 trial.

5 ACTING CHAIRMAN BERGFELD: Would it b e  
6 proper to assess that the discussion has led us to a  
7 division in the ulcers here as we consider th e  
8 microbial colonization infecti on, whatever it is, and  
9 that the diabetic ulcer is different than the venous  
10 and the dicubetous and in the venous and dicubetou s  
11 there may be more concern about infection? Docto r  
12 Cooper, would that be -- or do you apply all of what  
13 you said to all of the ulcer types?

14 DOCTOR COOPER: Well, in our clinica l  
15 setting, it's applied to all but I do understand the  
16 difficulty with the diabetic ulcer being a small ulce r  
17 unless you take it and make it larger and I am not an  
18 authority in diabetic ulcers. I take care of them .  
19 I study them in clinical trials with recombinan t  
20 growth factors, but I primarily am concerned about the  
21 venous ulcer and pressure ulcer.

22 DOCTOR LIPSKY: Could I ask a question of  
23 the FDA members. About a year ago, you had a  
24 conference where a bunch of this was discussed. I  
25 read the transcripts a while ago. One of the papers

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 that I hadn't previously read was one by Doctor Bendi  
2 from 1965 and that was discussed extensively. There  
3 were only two papers that were cited in that hundreds  
4 of pages of documents from that last session that  
5 talked about quantitative microbiology of wounds.  
6 Were any of you at that meeting last year and could  
7 you comment on what others have said?

8 DOCTOR MARZELLA: I think there appeared  
9 to be some sentiment that quantitative bacteriology  
10 correlated with outcome in the context of burns, but  
11 there was also consensus that there was no such  
12 agreement for chronic ulcers and that clinical  
13 outcomes such as reduction of infection or other  
14 increasing ulcer closures should be used  
15 preferentially to define a benefit rather than  
16 decreasing bacterial numbers. That was my  
17 understanding from what I heard.

18 DOCTOR LIPSKY: That was the way I read  
19 it, as well.

20 ACTING CHAIRMAN BERGFELD: Yes.

21 DOCTOR MUSTOE: I guess I just would - -  
22 Diane. I think that there are powerful theoretical  
23 reasons for believing that in fact bacterial levels,  
24 at least in many chronic wounds, are important because  
25 of the fact that we see lots of proteases in wounds.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 These proteases are derived from polys. There i s  
2 animal data which I presented that too many polys are  
3 deleterious to wound healing.

4 And I think that what Doctor Robson ha s  
5 done and Doctor Cooper have been a method o f  
6 stratifying wounds which I think from a theoretica l  
7 sense makes sense, but I also would agree that I thin k  
8 that the data is not there yet to say in fact tha t  
9 these wounds do differently although I believe tha t  
10 once the studies are done that you will se e  
11 differences. I think that what we're all saying abou t  
12 keeping the wound clean really is in essence keeping  
13 the bacteria count down which is a reflection o f  
14 inflammation. Inflammation is deleterious but I' m  
15 saying all this without, I think, the clinical studie s  
16 to back me up.

17 DOCTOR LIPSKY: I would only say that if  
18 the proteases come from the po lys, the polys are what  
19 makes -- and that suggests to me that clearly infecte d  
20 wounds need to be treated. If a wound is onl y  
21 colonized, there should be few polys there.

22 DOCTOR MUSTOE: There are lots of polys.  
23 I mean pus, it's a matter of d egree and yes, when you  
24 have frank pus, we'd agree that's infected. But I  
25 think you can do biopsies of chronic wounds and you'll l

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 see lots of polys in a wound that doesn't have pus .  
2 There are polys in the tissue and those polys, I would  
3 submit, without firm data to back me up, are at least  
4 in large numbers deleterious.

5 ACTING CHAIRMAN BERGFELD: Doctor  
6 Margolis.

7 DOCTOR MARGOLIS: At least for venous leg  
8 ulcers, I'm not really aware of any studies that have  
9 shown that bacterial burden or greater than 10<sup>5</sup> is a  
10 negative risk factor for healing at any period of time  
11 and there in fact some studies where patients were  
12 treated with intravenous and oral antibiotics in  
13 randomized controlled settings supposedly that were  
14 picked based on bacteria culture of other wounds  
15 quantitatively which showed no apparent effect on the  
16 rate of healing. So although I agree that bioburden  
17 seems like it should be important, I don't know that  
18 there's any great evidence, at least that I'm aware  
19 of, and I'd be really interested in seeing Doctor  
20 Cooper's paper that says that it's important for venous  
21 leg ulcers.

22 ACTING CHAIRMAN BERGFELD: Doctor Cooper,  
23 do you need to respond?

24 DOCTOR COOPER: Just briefly. I would say  
25 that I would concur that we do not treat with I V

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 antibiotics or systemically for these levels o f  
2 bacteria because the research has been done to sho w  
3 that those levels are not reached within the woun d  
4 which I said earlier today, but you treat the m  
5 topically with an antimicrobial that penetrates th e  
6 tissue is the way they are tre ated unless it's strep.

7 ACTING CHAIRMAN BERGFELD: Ms. Krasner.

8 MS. KRASNER: I just wanted to point out  
9 that the HCPR pressure ulcer treatment guideline #15  
10 that came out in 1994 addresses these issues fo r  
11 pressure ulcers extensively concerning biopsy an d  
12 culturing and David, you sat on that panel, so I  
13 suppose you could probably sum marize it better than I  
14 could.

15 DOCTOR MARGOLIS: I guess I could try .  
16 The person who would know the most is Georg e  
17 Rodehevers.

18 MS. KRASNER: He's gone.

19 DOCTOR MARGOLIS: It was his s ection that  
20 was working on it. I believe, as was mentione d  
21 before, that it was -- I don't think it was a categor y  
22 B. I thought it was a category C where the decision  
23 was made that if a wound didn't improve within fou r  
24 weeks, it should be biopsied for culture and if th e  
25 quantitative culture showed, I think, greater th an 10<sub>5</sub>

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 that it should be treated with antibiotics.

2 Again, I think that was based o n  
3 everybody's belief that it was important to assess the  
4 bioburden in the wound and I'm not sure that it wa s  
5 based on many randomized -- actually, I know it wasn' t  
6 based on any randomized clinical trials but that i t  
7 was based on many K series studies which would hav e  
8 given it a B rating. I'm pretty sure it was a C  
9 rating. I don't know if you have it with you. If it  
10 was a C rating, then it was based on a vote of th e  
11 panel which usually meant that it was based on whoeve r  
12 did that section, their belief.

13 ACTING CHAIRMAN BERGFELD: I think tha t  
14 you can make that guideline available to the FDA, if  
15 you don't mind, so they can review it.

16 DOCTOR MARGOLIS: I'm sure you guys have  
17 it.

18 ACTING CHAIRMAN BERGFELD: You have it?

19 DOCTOR MARGOLIS: Another governmen t  
20 branch.

21 ACTING CHAIRMAN BERGFELD: Docto r  
22 Eaglstein, did you have a comment?

23 DOCTOR EAGLSTEIN: As I said before, I  
24 think it was a B rating and there were two studies ,  
25 controlled studies. I think they were randomized.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DOCTOR MARGOLIS: Not for that document.  
2 Two randomized control studies would have gotten it an  
3 A rating.

4 DOCTOR EAGLSTEIN: Well, I think there  
5 were two --

6 DOCTOR MARGOLIS: A C rating usually means  
7 it --

8 DOCTOR EAGLSTEIN: My recollection is two  
9 studies to a --

10 ACTING CHAIRMAN BERGFELD: Well, we can  
11 clarify this later because we don't have the document  
12 in front of us.

13 ACTING CHAIRMAN BERGFELD: A C is, in my  
14 experience --

15 DOCTOR MARGOLIS: Yes, that's what a C  
16 rating was. That's what I thought it was. I just  
17 don't remember.

18 ACTING CHAIRMAN BERGFELD: I'm not sure  
19 that question four has totally been answered, but  
20 certainly we've discussed it and I think that there is  
21 some thought that ulcers can be infected chronically  
22 as well as acutely. When there's clinical evidence of  
23 infection, certainly quantitative measures and even  
24 surgical measures may be necessary to define the  
25 bacterial balance or the bacterial organisms or the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 microorganisms present.

2 The question arises whether in all ulcers  
3 should there be quantitative cultures before and a t  
4 some time distant in the thera py and certainly in the  
5 diabetic ulcer that appears to be not needed .  
6 However, in the venous ulcer and in the decubitu s  
7 ulcer there is some question and there is som e  
8 division of the panel members. So I think you'll hav e  
9 to sort that out. Yes.

10 DOCTOR ROSENBERG: We're not talking abou t  
11 therapy. We're talking about in the setting of a  
12 clinical trial.

13 ACTING CHAIRMAN BERGFELD: Yes. I know,  
14 but there was also a statement made that in th e  
15 beginning and at the end to assess the efficacy o f  
16 whatever was done in the antibiotic area fo r  
17 treatment, there would need to be two culture s  
18 beginning and sometime later. Do you have a comment?

19 DOCTOR ROSENBERG: No. I think w e  
20 shouldn't -- there are two issues. One is ho w  
21 patients should be taken care of and two is how they  
22 should be handled in the clinical trial when one i s  
23 trying to get information. They may not be just the  
24 same.

25 ACTING CHAIRMAN BERGFELD: That is true.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 That is true. Would you like to make a recommendatio n  
2 for a clinical trial?

3 DOCTOR ROSENBERG: No.

4 ACTING CHAIRMAN BERGFELD: I think it' s  
5 still quite unanswered for the venous ulcer and th e  
6 dicubetous ulcer.

7 DOCTOR ROSENBERG: I think one migh t  
8 expect -- if the agency were to demand rather mor e  
9 than a clinical trial best guidelines for care, I  
10 think it would be understandable.

11 ACTING CHAIRMAN BERGFELD: Fine. Ms .  
12 Cohen.

13 DOCTOR COHEN: Another subject. I wa s  
14 very disappointed yesterday that we were told that the  
15 trial, the clinical trials on white males. I can' t  
16 believe I'm discussing this, even saying it. I hope  
17 the FDA isn't doing lip service to it, but why do we  
18 have to keep repeating that it should be cros s  
19 cultural male/female, that it should be a true sample  
20 of today's society? And when I read that yesterday,  
21 I'm thinking I feel I'm back in the middle ages but i t  
22 should be gender. It should b e all these things that  
23 I thought the FDA was going to do and did do and I wa s  
24 very disappointed yesterday.

25 ACTING CHAIRMAN BERGFELD: Thank you for

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 that alert.

2           Anyone else make a comment? I think that  
3 we've concluded all that we can conclude under wound  
4 assessment topic and, therefore, we'll turn to topic  
5 six or question six. It deals with sterility of the  
6 product and there are three paragraphs here. "Th e  
7 sterility requirement or permissible bioburden level  
8 in association with the use of preservatives in a  
9 multi-use formulation for a topical product should be  
10 considered on the basis of the proposed indication and  
11 the route of administration. Although it is  
12 recognized that chronic ulcers are colonized, th e  
13 application of additional microbes may be detrimental .  
14 Sterility, therefore, is strongly recommended in the  
15 final formulation of topical products intended t o  
16 treat chronic cutaneous wounds."

17           I think we ought to stop there and ask if  
18 the panel or the committee thinks that is a true  
19 statement or a statement that is acceptable to them.  
20 And again, the part here that is somewhat debatable is  
21 whether they should be sterile products. Docto r  
22 Cooper.

23           DOCTOR COOPER: Well, I think afte r  
24 yesterday's presentation by Robert Wood Johnson that  
25 it was pretty evident that they met the criteria o f

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 USD as far as bioburden and it would seem excessive to  
2 have to go to sterility when they're going to be put  
3 on a wound that is colonized and they're frequently  
4 going to be used in outpatient settings. It's like  
5 overkill, I think.

6 ACTING CHAIRMAN BERGFELD: Is there any  
7 other comment that would disagree with that? No. I  
8 think then we can skip the second paragraph which  
9 deals with that issue about how you can achieve  
10 sterility because it appears in these chronic wounds  
11 which are usually distal on the leg or the foot that  
12 low bioburden is the achievable end point.

13 Third paragraph. "Are there indications  
14 for which sterility is less a concern than for other  
15 indications and for which a non-sterile product might  
16 be acceptable? If so, what level of bioburden would  
17 be acceptable and what specific microorganisms or  
18 family of microorganisms should be tested for  
19 exclusion in such a non-sterile product?"

20 I'd like to state that we have answered  
21 the first part of that question by saying that  
22 acceptable for the types of chronic ulcerations that  
23 we've discussed for the last two days would be a  
24 non-sterile product that had low bioburden but a  
25 definition of low bioburden should probably be

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 entertained at this time. Doctor Lipsky, Doctor  
2 Cooper?

3 DOCTOR COOPER: Well, I think that is  
4 already laid out by USP is my understanding and the  
5 organisms are listed. Is that true, Doctor Stromberg?

6 DOCTOR STROMBERG: The USP microbial  
7 limits test specifies that five objectionable  
8 organisms are absent and that, for the USP at least,  
9 the detection limit that is permissible is 100. The  
10 product we were dealing with yesterday had achieved  
11 less than 10 which was the limit of detection of that  
12 assay.

13 DOCTOR COOPER: I guess my question to you  
14 would be would you think that was adequate for the  
15 treatment of these kinds of ulcers as far as proof of  
16 bioburden? Not the 10 but I'm saying really assessing  
17 for what they're asking for as their criteria.

18 DOCTOR STROMBERG: No. I think our  
19 position is that we want it as low as feasibly  
20 possible and if it can be made non-detectable by one  
21 company, why can't it be made by another?

22 ACTING CHAIRMAN BERGFELD: And you would  
23 like us to endorse your position?

24 DOCTOR STROMBERG: Sure.

25 ACTING CHAIRMAN BERGFELD: Is there any

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 discussion of our panel members regarding this?

2 DOCTOR WITTEN: Or whether you have any  
3 other recommendations.

4 DOCTOR LIPSKY: I think what we can say  
5 for certain is that the product presented yesterday  
6 was safe and it was used on 900 and some odd patients .  
7 So we have a study that was done to show that a  
8 product that was aimed at reaching the US FDA  
9 recommendations was in fact safe to use on diabetic  
10 foot neuropathic. Was it their effort to exceed it or  
11 did it just happen that as they strove for that goal  
12 they over-achieved?

13 DOCTOR STROMBERG: No. There was a common  
14 sharing of purpose.

15 DOCTOR LIPSKY: And the question then  
16 would be how difficult is that? We're dealing with  
17 biological products and conceivably the steps that  
18 would be taken, heating and inactivation, to achieve  
19 this sterility might inactivate the biological  
20 products when we're looking at growth factors and so  
21 on. That would be my concern.

22 DOCTOR STROMBERG: I don't think we want  
23 to be specific about that. It depends on the product .  
24 We can't answer hypothetical settings.

25 DOCTOR LIPSKY: Well, that's what you've

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1       been asking us to do.

2                   DOCTOR STROMBERG: We've got it easier.

3                   ACTING CHAIRMAN BERGFELD: Any other  
4 comment? I think we're going to endorse your end  
5 point in some -- yes, Doctor Lynn.

6                   DOCTOR DRAKE: I mean I really respect  
7 Doctor Stromberg and I understand that, but I really  
8 have to support Doctor Lipsky's contention that it  
9 could undermine the product itself by sterilization.

10                   ACTING CHAIRMAN BERGFELD: No. That was  
11 low bioburden, not sterilization.

12                   DOCTOR DRAKE: Okay. So we're endorsing  
13 the low bioburden.

14                   ACTING CHAIRMAN BERGFELD: Low bioburden.

15                   DOCTOR DRAKE: All right.

16                   ACTING CHAIRMAN BERGFELD: Yes .  
17 Sterilization is out.

18                   DOCTOR DRAKE: Okay. Good.

19                   ACTING CHAIRMAN BERGFELD: Is there a  
20 concurrence of the committee --

21                   DOCTOR LIPSKY: Don't tell the World  
22 Health Organization.

23                   ACTING CHAIRMAN BERGFELD: -- on low the  
24 bioburden descriptors have been described by the  
25 committee and FDA? I think that we've come to the end

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 of all of the questions unless -- yes, Doctor Weiss.

2 DOCTOR WEISS: I just did not want to  
3 leave without addressing Ms. Cohen's earlier comment.  
4 No, no. I think it's a very good comment and it's  
5 unfortunate that we didn't have more discussion  
6 yesterday when the sponsor was here because certainly  
7 the agency promotes, as does most people, the idea of  
8 getting broad exposure in either gender and in the  
9 broad demographic base that's reflected by the people  
10 that are likely to have these conditions. How it  
11 ended up the way it did I can't answer that, but there  
12 was no exclusion, specific exclusion to exclude  
13 populations in the studies and I do think that's  
14 something that we need to look at and address perhaps  
15 post-marketing to gather broad experience. But it is  
16 something that's unfortunate we didn't discuss, I  
17 think, in more detail yesterday. But it something we  
18 need to really encourage.

19 DOCTOR HARKLESS: Yes. I think that  
20 Doctor Wilson raised that issue. I just think that  
21 the diverse -- as Ms. Cohen said, should reflect that  
22 and I think it's very easy if you make them more  
23 sensitive to those particular issues in the outset,  
24 you know, that it happens. I know he's a dean at Drew  
25 and he talked with the people at J&J and said if you

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 want to do this, let me know. I can contact all o f  
2 the black organizations -- I'm in a Hispani c  
3 environment. I know Hispanics all over the countr y  
4 involved in research --

5 ACTING CHAIRMAN BERGFELD: So are ther e  
6 any other general comments by anyone at the table ?  
7 The FDA, would you like to make a closing remark?

8 DOCTOR WEISS: I would just like to invit e  
9 this audience, both the committee and the audience, t o  
10 comment to this draft document that is out there. We  
11 are seeking comments, we are looking to put everythin g  
12 together into this first step. As I mentioned, I  
13 think, in my opening remarks of a draft guidanc e  
14 document and so we may not have addressed or you may  
15 think of additional things afterwards. There's a n  
16 appendix on pre-clinical issues that maybe some peopl e  
17 have some feelings about or experience towards and I  
18 would just invite people to make comments as the y  
19 think about these issues and submit them to the agenc y  
20 so that we can get all of your expertise.

21 DOCTOR HARKLESS: I'd like to thank Docto r  
22 Stromberg for inviting me. I'm not sure but I think  
23 it's probably one of the first times a podiatrist has  
24 actually been involved in this process and it's been  
25 very enlightening and I specif ically have an interest

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 in wound healing and I guarantee you that I'll know  
2 more because my chief of pathology is from Duke and  
3 I've already talked to him about wound healing and so  
4 we have a tremendous amount of information and  
5 knowledge to gain in that particular area in these  
6 patients who do not heal.

7 I also recommend that you include the Foot  
8 Care Council and the American Diabetes Association  
9 when you send out the comment for that. Send it to  
10 the ADA and I'm sure they'll send it to the Foot Care  
11 Council and the American Podiatric Medical Association  
12 may also want to comment.

13 DOCTOR WEISS: And on behalf of the  
14 agency, I would just like to thank the entire panel  
15 and consultants for their participation for the last  
16 few days and for your valuable comments.

17 ACTING CHAIRMAN BERGFELD: With those  
18 wonderful comments I, too, want to thank everyone for  
19 Doctor McGuire and myself. We are adjourned. The  
20 Advisory Committee meets tomorrow at 8:30 and so the  
21 Dermatological Advisory Committee will meet tomorrow  
22 in coordination or combination with the OTC panel.

23 (Whereupon, the meeting was adjourned at  
24 4:54 p.m.)

25

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701