



The CALGB Online

The CALGB has been working on improving various aspects of its informatics systems. In October 1996, the Central Office launched the new CALGB world wide web site on the internet. The new web site was formally introduced and demonstrated to the CALGB membership at several sessions of the Fall Group Meeting. It is designed to enable the Central Office to supply information to our members more efficiently and to provide easy access to frequently requested documents and information.

The web site consists of a public portion, which is available to the general public, and a section containing privileged information that is accessible only by CALGB members with a password. Please note that the only way you can obtain your password and user name is by visiting our web site at <http://www-calgb.uchicago.edu> and filling out and submitting an online request form. You will receive your password and user name within 24 hours. You must be a CALGB member to receive a password.

Another thing to keep in mind is that before you begin exploring the CALGB web site, you will need a software package called Adobe Acrobat, which is free and easily obtainable through the CALGB web site. This software allows us to present the information

exactly as it was created and lets you print the information or save it to your hard drive.

What's Available on the CALGB Web Site?

Meeting, publications, protocol, and administrative information is posted on the web site. Hyperlinks (highlighted text that will direct you to additional information) at the bottom of each section will provide a direct e-mail connection to the person who is in charge of that function at the CALGB Central Office.

Publications

- The *Cal Gab* and *CAPStone* newsletters.
- Minutes books.

Administrative

- Access to the CALGB roster database, searchable by name, institution, specialty, or member ID.
- *Policies and Procedures* manual.

Please note: Now that the manual is available online, the Central Office will no longer automatically mail out copies

Continued on Page 3

Inside:

CALGB Online	1
Message from the Group Statistician	2
Transitions	3
VA to Have Access to NCI-Supported Trials	4
Patient's Perspective	5
Oncology Nursing	6
Data Management	8
Protocol Updates	10
Group Meeting Report:	
Plenary Session Highlights	11
Informed Consent Research	13
Genetic Testing and Cancer	14

The Cal Gab is published quarterly by the Cancer and Leukemia Group B and distributed to the active membership.

Suggestions for articles are encouraged.

Copy deadlines are:

February 15, June 15, August 15, November 15

Articles should be sent to:

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**Please Note: While we make every effort to provide accurate dosing information in the Cal Gab, you should always check the appropriate drug dosages before prescribing and/or administering any medication.*

MAKE A NOTE

The new area code for the CALGB Central Office phone line went into effect Saturday, October 12, 1996. Please change the area code in your records and automatic dialing systems to 773. Callers can use either 312 or 773 until January 10, 1997, at which time the 312 area code will be disabled.

The CALGB Fax number will remain the same: 312-345-0117.

Message from the Group Statistician...

"Most people need all the help they can get to prevent them making fools of themselves by claiming that their favorite theory is substantiated by observations that do nothing of the sort. And the main function of...statistics...is to prevent people making fools of themselves."¹

It is a remarkable fact that the medical literature is replete with examples of the misuse or abuse of statistical methodology. Over the past 40 years, there has been a steady stream of papers assessing the statistical quality of papers published in a variety of medical journals. The findings have been remarkably consistent and disturbing: A large percentage of published papers contain errors in the use of statistical methods, and the situation has improved little over time despite increased attention to statistical refereeing.

"Approximately half the articles published in medical journals that use statistical methods use them incorrectly. These errors are so widespread that the present system of peer review has not been able to control them."²

Some of these errors are relatively harmless (such as the revealing typos reported by Doug Altman giving the results of an "impaired" t-test or an "arc sinus" transformation). Others are much more grievous errors, casting serious doubt on the major conclusions of the study.

One message from this statistician is that the reader of the medical literature should not rely on the peer-review system to reduce errors to an insignificant level. But how can one judge the quality of the statistics in a paper? And how can one avoid the pitfalls when preparing a manuscript? One answer is through the use of a statistical "checklist." Several have been published.³⁻⁵

The following is a two-part checklist that I use in refereeing medical journals and in preparing manuscripts reporting the results of clinical trials.

METHODS

Objectives: Were the objectives and major hypotheses stated?

Outcome measures (endpoints): Were the outcome measures defined?

Blinding (masking): Was blinding (masking) of treatments employed? If not, were the reasons given? If so, were details given? Who was blinded (patients, physicians, outcome assessors, etc.)? What were the methods used?

Eligibility: Were the eligibility and exclusion criteria given?

Source of subjects: Did the subjects come from a single institution (clinic) or from multiple institutions? Were the participating institutions listed?

Registration and randomization: Was the registration process managed and controlled separately from those who registered patients? Was there a random allocation of patients to treatment? What were the details of the randomization design? What mechanism generated the random assignment?

Quality control and quality assurance: What were the mechanisms for ensuring data quality? Was there an independent review mechanism for assessing eligibility, response, and toxicity? Were there any random audits of the source documents?

Dates: Were important dates given (e.g., date the study opened, date the last patient was admitted, and approximate date of analysis)?

Sample size (planned): What was the planned number of subjects and what were the reasons for this planned number (e.g., power and size of detectable difference)?

Monitoring: Were there any plans for formal monitoring or interim analyses of the trial in progress? How was this accomplished?

RESULTS

Patient accounting: Were all registered patients accounted for in the analysis?

Patient characteristics: Were the treatment groups comparable in relevant

patient characteristics? Were prognostic factors considered?

Treatments: Was there an assessment of compliance to the treatment regimens, including both patient compliance (e.g., for self-medications) and physician compliance (e.g., for surgery, radiotherapy, and chemotherapy)? Was there a summary comparison of planned vs. actual treatment? What proportion of patients completed treatment?

Toxicity: Were toxicity, side-effects, and complications discussed?

Sample size (actual): What was the difference between the planned and actual sample size? Why was the study stopped and reported now? Was statistical power or precision addressed for "negative" studies?

Follow up: Was there an accounting for the number (and timing) of patients who were lost to follow up or who dropped out? Were the reasons for these losses given? Were the losses given separately by treatment group? Was it clear how these patients were treated in the analysis? Were the reasons for "censoring" given? What was the duration of follow up (e.g., median, percent at various time points)?

Statistical analyses: Was enough detail provided to enable a reader to reproduce the analyses if the data were available? Were all statistical methods defined and identified? Were references given to standard sources (with page numbers)? Were computer programs identified and referenced? Were measures of precision and uncertainty presented (e.g., standard errors, confidence intervals, or other measures)? Were regression models validated?

General: Were the conclusions drawn appropriate and justified from the design and analysis presented?

Of course, any paper properly addressing these questions is not necessarily a good paper and may not even be well written. Such a paper, however, has at least passed a test that few published papers have passed.

Stephen L. George, Ph.D.

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CALGB Online
Continued from Page 1

to new members (we will still send a copy upon request). If you need a copy, please download it from our web site.

Meetings

- Core and Group meeting information.

Protocols

- Protocols activated from August 15, 1996, to the present—updated monthly.
- Model consent forms.
- Protocol Updates—updated monthly.
- Protocol Status Sheet—updated monthly.
- Historical protocol index listing protocols from the Group's inception.

News

- Postings of general information for CALGB members.

The web page is intended as an additional distribution method and will not take the place of materials our members are currently receiving. You will continue to receive your protocol mailings, broadcast e-mail messages, and the newsletters.

We urge you to check out our new home page. The web site address is: <http://www-calgb.uchicago.edu>. This will take you to the CALGB home page, where you can request a password or enter the members-only site if you already have been issued a user name and password. If you have any questions or concerns specific to the web page, the web server also has an e-mail address: calgb-web@uchicago.edu

Transitions

We would like to welcome the following individuals to the CALGB:

CALGB CENTRAL OFFICE

Diane Haywood joined the staff in October 1996 as the new Executive Secretary. Before coming to the CALGB, Ms. Haywood worked at the University of Chicago in the Department of Sociology. Her phone number and e-mail address are: (773) 702-9171; dhaywood@midway.uchicago.edu

Alicia D. Ware is the new Audit Coordinator at the Central Office. Ms. Ware earned a B.S. in biology from the University of Illinois, Champaign. Prior to her employment with the CALGB, she served as a Quality Assurance Coordinator for LifeSource Blood Services. Ms. Ware's phone number and e-mail address are: (773) 702-9973; aware@midway.uchicago.edu

CALGB STATISTICAL CENTER

Susan Halabi, who has a Ph.D. in biometry, will be the Statistician for the Prostate and the Cancer Control Committees. Her previous appointments were with the Tulane Cancer Center, School of Medicine and the Department of Biostatistics and Epidemiology, School of Public Health and Tropical Medicine. She also worked at the University of Texas M.D. Anderson Cancer Center.

CALGB DATA MANAGEMENT CENTER

Kyla Meg Dana has been appointed to the position of Data Technician at the Data Management Center (DMC) and will be working with leukemia studies. Ms. Dana received a B.A. in biology from the University of North Carolina at Asheville. She has also worked as a temporary data technician with the DMC.

Robin Heinze is a new Data Technician at the DMC. She will be involved with breast and lymphoma studies. Ms. Heinze was awarded a B.A. in Biology from Randolph-Macon Woman's College. She previously worked as a temporary data technician with the DMC, served as an information specialist with the CDC National AIDS Hotline, was a research assistant at the Clinical Breast Cancer Lab at Bowman Gray Hospital, and was an intern with the Lynchburg Family Practice Residency Center.

The DMC welcomes **Dana McDonald** to the position of CALGB Registrar. Ms. McDonald comes to us from the Bone Marrow Transplant Department at Duke University Medical Center. She graduated from Duke University with a B.A. in psychology and has worked in management positions with Robert Taylor Associates in Chapel Hill and Ben & Jerry's Ice Cream.

Gertrude Elion Cancer Research Award

The American Association for Cancer Research (AACR) is accepting nominations for the annual Gertrude Elion Cancer Research Award. This award is provided through an educational grant from Glaxo Wellcome Oncology and is presented to a nontenured scientist at the level of Assistant Professor engaged in meritorious basic, clinical, or translational cancer research at a nongovernment, not-for-profit research facility. Acceptable research sites include medical centers, cancer centers, universities, teaching hospitals, or academic research institutes in the United States or Canada. The one-year, \$30,000 award recognizes research excellence in cancer etiology, diagnosis, treatment, or prevention.

For further information on the application process or Award criteria, or to request an application form, contact: Gertrude Elion Award Coordinator, American

New Phone Number and Address for the CALGB Statistical Center

The statisticians in the CALGB Statistical Center have new telephone and fax numbers and a new mailing address. **Please note:** these changes affect the statisticians only. There are NO changes for the data operations or information systems staff and NO changes to the address for sending data forms or to the telephone number for patient registrations. Also, all e-mail addresses are unchanged.

The new address, phone, and FAX numbers are:

CALGB Statistical Center
P.O. Box 2915
Durham, NC 27715-2915

Phone: (919) 681-2224
FAX: (919) 681-8028

VA to Have Access to NCI-Supported Trials

Effective January 1, 1997, an interagency agreement will be in place between the Department of Veterans Affairs (VA) and the National Cancer Institute (NCI) that establishes a partnership in clinical trials for cancer. The agreement will expand the existing relationship between the VA and the NCI into a more formal and extensive partnership. The primary purposes of the partnership are to increase the access of eligible veterans to NCI-sponsored trials—which include those reviewed and approved by NCI staff; NCI cooperative group studies; studies that are conducted in clinical and comprehensive cancer centers under an NCI-approved protocol review and surveillance mechanism; and protocols performed under the direct support of an NCI peer-reviewed grant—and to provide VA clinical investigators with expanded opportunities to participate in clinical cancer research.

The major benefits of this agreement are:

- eligible veterans nationwide will gain access to promising new approaches to diagnosis, treatment, and prevention available on NCI-sponsored studies. In particular, a close working relationship with the VA's primary-care delivery system will facilitate access to patients and physicians interested in participating in diagnostic and prevention efforts;
- the NCI's clinical trials program will realize a potentially significant increase in accrual rates, which will in turn result in more timely completion of these studies;
- VA clinical investigators will have expanded opportunities to participate in clinical cancer research;
- the cancer center and cooperative group clinical trials programs will be strengthened with the expanded pool of VA cancer researchers; and
- involvement of the NCI and the VA in each other's planning of clinical research will improve the quality and efficiency of planning in both agencies.

The new agreement will be implemented through several types of affiliations, depending on the capabilities and interests of the individual VA hospitals and their staffs. Individual VA institutions will be considered for the group membership status that is most appropriate for their own circumstances, including main membership; participation in the NCI's CCOP program; or affiliate membership. All VA facilities providing oncology services will be allowed to apply for participation in the NCI cooperative group program. Veteran's Administration hospitals that are part of academic medical centers will be allowed more extensive participation in the NCI's early clinical trials program. Under special circumstances, such as trials of particular importance to the VA or trials of rare tumor types, eligible veterans may be offered access to NCI-sponsored clinical trials in nearby civilian facilities participating in such studies. Closer linkages will be possible under the new agreement between the cancer planning activities in the VA's Cooperative Studies Program and the NCI clinical trials program. While such cooperation

currently exists to a degree, for example, through the joint sponsorship of the PIVOT trial in early prostate cancer, expanded participation between VA experts and NCI investigators and staff in developing future trials in a variety of malignancies will strengthen the planning efforts of both entities. Cost effectiveness evaluation is of increasing importance to investigators in both the VA and the NCI, and the linkages between the two organizations should prove beneficial in developing and initiating an agenda based on mutual research goals and addressing economic research questions.

ACKNOWLEDGMENTS

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 Janssen Pharmaceutica Research Foundation
 Leukemia Clinical Research Foundation
 Lilly Oncology
 Merck U.S. Human Health
 Myriad Genetic Laboratories, Inc.
 Nexstar Pharmaceuticals
 OncorMed, Inc.
 Ortho Biotech Inc.
 Pfizer Inc.
 Pharmacia & Upjohn
 Rhône-Poulenc Rorer Pharmaceuticals Inc.
 Sandoz Oncology/Sandoz Pharmaceuticals
 Schering Corporation
 SmithKline Beecham
 Strato/Infusaid, Inc.
 T.J. Martell Foundation for Leukemia,
 Cancer and AIDS Research
 Vince Lombardi Memorial Classic
 Vysis/ATC Diagnostics, Inc.

PATIENT'S PERSPECTIVE

Bringing the Real World into Clinical Trials

by Deborah Collyar, President
Patient Advocates In Research (PAIR)

Accrual plagues clinical researchers so much that it quickly becomes a mantra to all who enter the clinical trials arena. It isn't difficult for those who are determined to learn more about the research process to figure out how important clinical trials are. They remain the best way to find better treatments and interventions for people with cancer. Obviously, though, in order to find better therapies, we have to attract people to clinical trials before those therapies can become standard practice.

I am constantly amazed, however, at how little is done to improve accrual to trials. This perhaps stems from the same "status quo point of view"—that limited funding for research is an irrevocable fact of life—of researchers who still lament when it's time to put a grant together for funding. After studying the accrual issue for the last few years, I've come up with some ideas that will surely stimulate lively debate.

First, let's start with a disturbing fact of life: The public thinks that the purpose of funding for cancer research is to make people's lives better, and to be fair, most cancer researchers believe that is what they are doing. Research entities, however, view funding as a way to stay in business. This may sound harsh, but research-based institutions operate on the premise that research dollars should support their substantial overhead fees. While I don't suggest we obliterate the whole system, we definitely need to strive for a better balance between these opposing positions. The question should not only be "where is the money going to come from?" but also "how can we improve our results?" Today's changing health-care system has thrown a monkey wrench into the institutional philosophy and has created many opportunities to look at innovative approaches when conducting quality clinical research.

Historically, clinical trials have been approached from an almost exclusively scientific perspective. Virtually no thought was given to patients until after the trial was designed because that was

when people needed to be recruited to answer the scientific question(s), publish an article, and hopefully to influence community practice. Since conducting research on human subjects is the reason we fund clinical trials, I propose we consider the human subjects as an underlying test of validity in designing clinical trials, in addition to (not in place of) scientific validity. Another advantage to this approach is that managed-care entities seem more open to support methods that provide "practical solutions." Practical solutions are, and always have been, the only ones that gain wide acceptance.

Infusing people into the Process

Clinical researchers are, in reality, providing a service (i.e., clinical trials) that they want people to use (i.e., accrual). Following are some fundamental principles that must be applied when you want to attract people (i.e., human subjects) to your service:

- Learn what *their* needs and motivations are, not *yours*.
- Design your trial to meet as many of *their* needs as possible (you'll automatically cover your own needs).
- Show them what value *they* will receive, not what *you* will get out of it.
- Improve protocols with feedback on areas *they* think are important, not exclusively on *your* issues.
- Take responsibility to help patients find resources that will allow them to participate in your trial.

A natural human reaction to almost anything we are told is "so what?" This is commonly referred to as WIIFM: what's in it for me. Governments, institutions, health-care professionals, and even patients do it. So how do you build what some consider a human character flaw into the scientific equation? You do it by going directly to patients, instead of studying what health-care pro-

fessionals think people need or want.

Needless to say, there are ramifications to my proposal. We will have to change the way we design clinical trials to include patient-oriented variables. Many trials now have patient barriers built into them because their needs weren't considered. The way we perform clinical trials will also have to change, from informed consent to how treatment and interventions are applied. One more critical change lies in how we evaluate trials, by providing an open feedback loop to make future trials more successful.

Food for Thought

Let's wave a magic wand, and assume the accrual rate actually increases. Here are some questions to consider:

- How prepared are we to handle it?
- How do we keep pace with clinical trials that close within a year instead of five to ten years?
- Can we come up with clinical trials that would interest a larger audience?
- How many people do we really need?
- Are there different approaches we can take to utilize more people and get more questions answered?

Many changes will take place within the clinical trial process in the next few years. These changes will be dictated by outside forces unless you take a proactive approach right now. The CALGB has started to take a lead role by including patient advocates in the process. Let's work together to make trials more interesting and feasible for potential participants. It may just help us find more timely answers for those who need them the most—people with cancer.

Comments or topics you would like to see covered may be directed to:

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ONCOLOGY NURSING

Nursing Implications of Isotretinoin and Tretinoin

by Kerry Cassone, R.N., O.C.N.
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Retinoids—*isotretinoin* and *tretinoin*—are vitamin A derivatives capable of modulating the growth and differentiation of normal, premalignant, and malignant cells.^{1-4,6,7} The exact mechanism of their anticancer effect is not known.^{7,10} *Isotretinoin* (13-*cis* retinoic acid, Accutane®) is available in oral form for antineoplastic use only through clinical trials. It is being studied in various settings including CALGB and Intergroup studies.^{1,4,6,7} *Tretinoin* (all-*trans*-retinoic acid, TRA, all-TRA, Vesanoid®) is approved for treatment of acute promyelocytic leukemia (APL) patients for remission induction. There is a particular challenge to nurses in the management of these patients as disease entities treated with these drugs vary widely. The nursing implications of retinoid administration will be addressed here. (The following information pertains to both *tretinoin* and *isotretinoin* unless otherwise specified.)

HOW SUPPLIED

No special handling is required.¹

Isotretinoin:

For antineoplastic use through clinical trials only.

Capsule: 10 mg, 20 mg.

Tretinoin:

Capsule: 10 mg.

Onset/duration:

Isotretinoin: peak 3.2 hrs; half life 10-20 hrs.⁹

Tretinoin: peak 1-2 hrs; half life 0.5-2 hrs.¹⁰

INDICATIONS AND DOSAGE

Tretinoin has recently been approved for use for induction of remission in certain APL patients. Phase I-III clinical trials also utilize *tretinoin* and *isotretinoin* as antineoplastic agents for a wide range of hematologic and oncologic malignancies.^{2,4,7} These drugs

are also being studied in combination drug settings.

Oral dosing is once or twice a day. Dose and frequency are dependent on the setting or clinical trial.¹

Tretinoin:

Absorption is increased when administered with a fatty meal.¹

Adult/APL: 45 mg/m²/day divided into two doses. Continue therapy for 30 days after CR is achieved, or after 90 days of total treatment, whichever occurs first.¹⁰

For other diseases, doses are study dependent. Doses up to 100 mg/m²/day for adults well tolerated; MTD 195 mg/m²/day due to mucocutaneous toxicities.^{2,10}

Pediatric: 45 mg/m²/day.¹

Isotretinoin:

Absorption is increased if taken with food.⁹

Adult: 10-60 mg/m²/day^{4,7} or 0.1-6.0 mg/kg/day,⁶ study dependent.

ADVERSE REACTIONS

See Table 1, next page.

TREATMENT OPTIONS FOR ADVERSE REACTIONS

For moderate or severe toxicities:⁷

Dose reduction, delay, or discontinuation^{1,7} is initiated depending on the type and severity of the toxicity. Vitamin E 200-800 mg/day has also been used.⁷

For Retinoic Acid Syndrome (RAS):

The treatment of choice is dexamethasone 10 mg IV at the first sign of RAS (see Table 1), then q 12 hrs. for a minimum of three days or until resolution of symptoms.^{2,10} Patients will need hospitalization and close monitoring during this period.

INTERACTIONS

Avoid dietary vitamin A supplementation.¹

Tretinoin:

Do not give concurrently with medications that affect the P450 system such as phenytoin, barbiturates, carbamazepine, rifampin, cimetidine.¹ There can be a change in the serum level of *tretinoin* with concurrent use of *ketaconazole*.¹⁰

CONTRAINDICATIONS

Contraindicated with pregnancy. Do not give to any patient who exhibits hypersensitivity to any component of the drugs' components; particularly, with *tretinoin*, is parabens which are used as preservatives in the gelatin capsule.¹⁰

NURSING CONSIDERATIONS

Patients should not be pregnant at initiation of drug and should maintain adequate birth control measures.¹⁻⁶ Severe fetal malformations have been noted even with a single dose of *isotretinoin* and with subtherapeutic doses of *tretinoin*.^{3,10} Contraception must be used even with a history of infertility or menopause unless a hysterectomy has been performed.¹⁰ It is recommended that two reliable forms of contraception be used, unless abstinence is the chosen method.¹⁰ Patients should be instructed to stop the drug at least one month prior to conception.^{6,10} Pregnancy testing and contraceptive counseling should be done every month during therapy and for one month post-therapy.⁹

Instruct patients to maintain a current list of concomitant medications⁶ and bring this list to each clinic visit. Patients should check with their physician before taking any new medication and dietary supplements.

Instruct patients to take *tretinoin* with fatty meals¹ to increase absorption.

Isotretinoin should be taken with a meal.⁹

ONCOLOGY NURSING

Monitor CBC, coagulation studies, liver function tests, and serum triglycerides regularly.¹⁰

Instruct patient to report any symptoms to their physician immediately.

Carefully monitor APL patients for signs of respiratory compromise, RAS, and/or leukocytosis.¹⁰

Patients may need frequent follow

up contact to ensure compliance, as well as to monitor toxicities.

Summary

Nurses can make a significant impact on the care of patients under treatment with isotretinoin and tretinoin. With the approval of tretinoin for APL and the

continuing clinical trials for both drugs, nurses will be increasingly involved with these patients. Patients need ongoing assessment of medication tolerance, side effects, and psychosocial adjustment to their disease and treatment. Thus, there is a real need to stay updated regarding the nursing management of patients undergoing these treatments.

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Table 1. Side effects of retinoic acid therapy

Abbreviations: VLDL, very low-density lipoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ESR, erythrocyte sedimentation rate.⁶ APML, acute promyelocytic leukemia.¹

DATA MANAGEMENT

Institutional Performance Evaluation Committee

by Sherry Breaux, CALGB Quality Assurance Coordinator

The CALGB monitors the performance of its member institutions through the activities of the Institutional Performance Evaluation Committee (IPEC). IPEC members currently evaluate institutions semiannually using information submitted by the Data Management Center (DMC), the Data Audit Committee, and the Quality Assurance Review Center (QARC). The IPEC is responsible for the ongoing review of institutional performance to ensure sufficient institutional participation and quality of data submission. In this role the Committee alerts institutions to deficiencies in accrual and data quality, and brings persistent problems to the attention of the Chair of the Membership Committee and the Central Office.

The *CALGB Policies and Procedures* manual outlines the methods used by IPEC, the Data Audit Committee, and QARC. The following material supplements the *CALGB Policies and Procedures* manual by providing expanded definitions of terms used in IPEC reports, answers to commonly asked questions, and a review of comments from recent evaluations.

IPEC Review of Institutional Participation

Main member networks are required by the CALGB to have 65 accruals per year; affiliates must register at least 6 cases annually. Both main member networks and affiliates must attain the required accruals within 24 months of membership. The Data Management Center (DMC) provides the IPEC with semiannual reports of accrual by CALGB main members and affiliates during each of the last five calendar years. Main member institutions or affiliates with fewer than the required number of accruals during the most recent 12-month period covered by the report are considered to have unacceptable accrual performance. Trends are also observed, and a main member is advised in writing if the IPEC notes that annual accrual is dropping and is nearing an unacceptable level.

The accrual tables submitted to the

IPEC by the DMC differ from those found in the semiannual agenda book produced for the Group Meeting. The agenda book tables cover the 12-month period ending two months before the Group Meeting. An agenda book table reporting monthly accrual by institution during that time period is sometimes used by the IPEC to observe recent monthly trends in accrual.

IPEC Review of Timeliness of Data Submission

The DMC compiles semiannual reports for the IPEC that show the delinquency of data submission from institutions participating in CALGB-coordinated treatment studies. The reports summarize the status of submission of *survival data* and *clinical status data* for patients entered in each of the four calendar years before the last full calendar year for each main member network. The last calendar year is deleted because of insufficient follow-up potential.

Delinquency reports measure the timeliness of submission of survival data as well as clinical status data. Survival and clinical status data delinquency percentages are calculated for each main member network for specified registration time periods. In other words, the delinquency percentages are reported and credited to the time period in which the patients were registered. The method for calculating each percentage is described as follows:

Clinical status delinquency percentage:

$$\frac{\# \text{ of alive pts. who have not reached study endpoints and who are delinquent for clinical data}}{\# \text{ of alive pts. who have not reached study endpoints}} \times 100$$

Survival status delinquency percentage (alive patients only):

$$\frac{\# \text{ of alive pts. who are delinquent for survival data}}{\# \text{ of alive pts.}} \times 100$$

One month before the final IPEC reports are run, the DMC sends main member institutions *preliminary (preview) lists* of patients with delinquent data from their network. If complete data for the delinquent patients are received by the DMC before the deadline indicated in a letter accompanying the lists, these patients will not appear as delinquent in the final reports sent to the IPEC. It is important to note that the program that generates the report is run on the dynamic CALGB database, not a frozen data set. A few patients may appear in the final IPEC report who have become delinquent since the preview report was run. Usually there are no more than six additional delinquent patients per cycle in the Group.

Copies of the final reports presented to the IPEC are sent to the institutional PI and lead Clinical Research Associate within the month after the Group Meeting.

There are several points which are important to understand about the preview and final lists.

- The *cutoff date* and *report date* are created by the report program.
- The *cutoff date* is a date roughly halfway through the review cycle that is used as a point of reference in determining delinquency. It is not the date that the report is run. Preview and final reports are run in a cycle using the same cutoff date.
- The *report date* is the date that the report is run. It appears at the bottom left corner of the report. This date will differ between the preview and final reports.
- For a patient who has not yet reached the protocol endpoint (for older studies, this means "off-study"), the case date is the last date covered by a case report form submission that is complete with respect to study endpoint information. (Common study endpoints are local or distant recurrence, disease progression, or death.) The completeness of the clinical data submission for such a patient determines whether the case date can be

DATA MANAGEMENT

updated. If a data submission's information about the endpoints is incomplete, the Data Coordinator cannot use the data to update the case date. Since the case date is used to calculate clinical status delinquency, incomplete data submission may cause the patient to appear on the delinquency list (and increase the delinquency percentage).

If forms or data are missing that are required by the protocol but are not required for assessment of endpoints, the study Data Coordinator updates the case date and requests that the institution send the omitted data. These data omissions should not affect the clinical status delinquency percentage.

If a patient appears on the institutional preview list as delinquent for clinical status data and the data management staff at the institution is certain that the data were sent, it is important for the institution to contact the study's Data Coordinator to determine if the data were received at the DMC but were incomplete. *Do not just resend the same data forms without checking* with the data coordinator(s) responsible.

Following an incomplete data submission, if a subsequent clinical data submission offers sufficient information about the endpoints, and there are no outstanding or unresolved queries from the Data Coordinator about the endpoints, the case date can be updated to reflect the new data submission.

- If a patient is declared lost by the institution, despite the efforts of the institution to locate the patient, the IPEC considers the patient to be delinquent and the patient will continue to appear in delinquency tables during the four-year window. CALGB policy requires that a patient be followed until death.
- Data for patients who have withdrawn consent for survival or clinical follow-up are not considered delinquent, provided that the institution has sent the DMC the required documentation, signed and dated by the patient. (See section 8.1.2 of the *CALGB Policies and Procedures* manual for additional information.)

IPEC Review of Institutional Data Quality

The IPEC requires specific documenta-

tion of the quality of institutional data submission in order to evaluate performance. To meet the needs of the IPEC and to provide feedback to CALGB institutions, Data Coordinators perform supplemental detailed evaluations on specific cases randomly selected twice annually using a program designed by the CALGB Statistical Center. The use of selection criteria, indicated in section 2.9.1.1 of the *CALGB Policies and Procedures* manual, results in a list of patients who have adequate data submission for review, and whose data have been submitted by recent or current institutional data management staff. These evaluations (using the I-008 form) form the basis of semiannual reports to the IPEC on institutional data quality, one cycle reflecting the performance of the main member institution and the second reflecting affiliates' performances.

Copies of completed evaluation forms are sent to the PI and Lead CRA at the main member by the DMC approximately one month before the final reports are run. The PI or CRA should contact the Data Coordinator who completed the form if there are questions about the evaluation. The Data Coordinator may amend the evaluation if a change is supported by the comments from the institution. If there are unresolved questions about an evaluation, the institution may send a letter to the Quality Assurance Coordinator, who will include the comments in the report to the IPEC.

The I-008 form focuses on completeness, consistency, and legibility of the data submitted on coded forms and flowsheets. The I-008 form has been revised for the Fall 1996 cycle to include a Likert scale of 1-3 (instead of 1-5) for all questions, with "1" being the best score possible and "3" being the worst. Whenever a score is greater than "1," the Data Coordinator must comment on the data items or forms that are missing, inconsistent, or illegible.

A review of the comments made by the Data Coordinators in the spring 1996 cycle indicates that the following areas are sources of problems found in the evaluations of data quality. In looking at these numbers, consider that 300 cases were reviewed for this cycle.

- Of 41 comments referring to problems with the *completeness of on-study data*, almost half (19 comments) indicated that

operative or pathology reports were not submitted with the on-study form. In five (12%) other cases, comments referred to missing measurement forms; in another five (12%), flowsheets were missing.

- The greatest number of problems (139) occurred with *completeness of follow-up forms and flowsheets*. In 17 (12%) of the cases, no forms had been submitted. In 98 (70%) of the problem cases, one or more follow-up forms or flowsheets had been submitted late or were still missing (59 more than one year late, 39 less than one year late); in 16 of these late submissions, toxicity forms were specifically mentioned, and in another 11 (8%) either a C-113 (Notification of Death Form) or required flowsheets at death were not received. The wrong form was submitted in 11 (8%) instances.

- In reviewing the *completeness of specific data items*, 105 problems were cited. Almost one-third (33) of the comments said that the CALGB patient ID number had been omitted from the form or had been entered incorrectly. Missing or incorrect patient numbers can result in lost data. Another 19 comments cited a lack of numbering of flowsheets or missing dates. These items, perhaps seemingly trivial, can present problems for the Data Coordinators who are trying to follow the patient's progress chronologically.

- Another area in which problems were found (84) was in *documentation on the flow sheet to support data found on the coded forms*. The most frequently cited missing documentation was for toxicities (17, or 20%), prestudy data (12, or 14%), and body surface area/height/weight (12, or 14%).

Proposed Additions to IPEC Reviews

The Surgery and Correlative Sciences Committees have drafted procedures to review the performance of CALGB institutions in studies with surgical or correlative sciences components. The input by these two committees has become part of an IPEC document that outlines evaluation procedures and defines acceptable institutional performance. This document has been submitted to the Executive Committee for approval.

PROTOCOL UPDATES

❖ Activations

◆ 8/15/96

CALGB 9550: Low-Dose Interleukin-2 in AIDS Lymphoma—A CALGB Pilot Study. Study Chair: Michael Caligiuri, M.D.

CALGB 9680: A Phase II Trial of High-Dose Mitoxantrone/GM-CSF and Low Dose Steroids in Patients with “Hormone Refractory” Stage D2 Carcinoma of the Prostate. Study Chair: Ellis Levine, M.D.

CALGB 9631: High Dose Doxorubicin with Recombinant Granulocyte Macrophage Colony Stimulating Factor(GM-CSF) Plus Dexrazoxane for Malignant Mesothelioma: A Phase II Study. Study Chair: Michael Kosty, M.D.

CALGB 9583: A Phase III Two-Arm Randomized Study Comparing Antiandrogen Withdrawal Alone Versus Antiandrogen Withdrawal Combined with Ketoconazole and Hydrocortisone in Patients with Advanced Prostate Cancer. Study Chair: Eric Small, M.D.

◆ 10/15/96

CALGB 9633: A Phase III Study of Adjuvant Chemotherapy After Resection for Patients with T2N0 Stage I Non-Small Cell Carcinoma of the Lung. Study Chair: Gary Strauss, M.D.

CALGB 9671: Long-Term Psychosocial Adaptation of Survivors of Breast Cancer Treated by Adjuvant Chemotherapy Fifteen Years Ago (Companion to CALGB 7581 [Closed]). Study Chair: Alice Kornblith, Ph.D.

◆ 11/15/96

CALGB 9650: Pharmacodynamic Modeling of Oral Etoposide in Relapse Non-Hodgkin's Lymphoma (IWF Grades A-H): A Phase II Study. Study Chair: Nancy Bartlett, M.D. Study Co-Chair: Antonius Miller, M.D.

❖ Closures

CALGB 9364: Effect of Bereavement on Disease Recurrence and Death in Women with Stage II Breast Cancer (Companion to CALGB 8541 [closed]). Study Chair: Jimmie Holland, M.D. (9/15/96)

CALGB 8961: RAS Mutations in Myelodysplasia. Study Chair: Edison Liu, M.D. (9/30/96)

CALGB 9155: Treatment of AIDS-Associated Non-Hodgkin's Lymphoma with Cyclophosphamide/Doxorubicin/Vincristine/Prednisone/Etoposide (CHOPE), Zidovudine, Granulocyte-Colony Stimulating Factor (rhG-CSF), and Erythropoietin (rhEPO). Study Chair: Carl Freter, M.D., Ph.D. (9/30/96)

CALGB 9113: Allogeneic Bone Marrow Transplantation for Patients with Poor Prognosis Acute Lymphocytic Leukemia: A Phase II Trial. Mandatory Companion: 8762. Study Co-Chairs: Charles Linker, M.D., and Michael Schuster, M.D. (10/15/96)

CALGB 9462: Phase I Study of Continuous Infusion Topotecan and Weekly Cisplatin in Patients with Advanced Cancer. Study Chair: Rogerio Lilenbaum, M.D. (11/15/96)

SEEKING ACCRUALS?

The Central Office suggests the following “enrollment-friendly” protocols:

CALGB 9365: PHARMACOGENETICS OF 5-FLUOROURACIL

Eligibility:

Cancer patients with colorectal carcinoma who will be treated with 5-Fluorouracil (5-FU) either alone or in combination with other therapy on CALGB protocols 9294, 9395, 9483, 9491, or 9498 and future adjuvant chemotherapy trials for colon or rectal cancer.

Sample Collection: A blood sample (25 ml) will be collected prior to beginning the first 5-FU infusion.

CALGB 9371: A WEIGHT LOSS PROGRAM OF WOMEN WITH BREAST CANCER: A PILOT FEASIBILITY STUDY

Eligibility:

- Women with a diagnosis of Stage I, Stage II breast cancer and are considered to be overweight (>10% over ideal body weight).
- Must be enrolled **prior** to beginning **ANY** adjuvant chemotherapy or radiotherapy regimen (patients do **NOT** need to receive their adjuvant therapy on a CALGB study).
- **Blood draw required prior to beginning adjuvant therapy**, prior to beginning weight loss program, and at completion of weight loss program.

Procedure: Patients that fit the above criteria will join the Weight Watchers Program (**free of charge**) in their geographical area following adjuvant therapy.

CALGB 9662: CLONALITY ANALYSIS IN PATIENTS UNDERGOING AUTOLOGOUS BONE MARROW TRANSPLANT FOR NON-HODGKIN'S LYMPHOMA

Eligibility:

Female patients registered on CALGB 9254. All female patients registered to CALGB 9254, whether they proceed to randomization or not, may be enrolled on CALGB 9662.

Sample Collection: At the time of registration, transplant, and then at 6 months, 1 year and q 4 years post transplant 20cc of blood will be drawn. These timepoints coincide with the normally scheduled sample collections that occur in CALGB 9254.

1996 FALL GROUP MEETING

Plenary Session Opening Remarks

Group Chair's Remarks

At the Fall Group Meeting, Dr. Richard Schilsky, CALGB Group Chair, commented on some of the changes that have occurred at the Committee level within the CALGB.

The Clinical Economics Committee is the most recent committee to be formed as a full committee, gaining approval by the Board of Directors at the May Group Meeting.

Recently, the CALGB appointed an AIDS Malignancies Working Group and received supplemental funding from the NCI to support this new initiative. Protocol 9550, which tests IL-2 for patients with AIDS-related lymphomas, has been developed and will be conducted collaboratively with the AIDS Malignancies Consortium.

The CALGB has restructured the Solid Tumor Correlative Sciences Committee. It was decided to formally develop Correlative Sciences Working Groups for each of the solid tumor areas studied by the CALGB. There are representatives on the Committee from the disciplines of tissue procurement, pathology, epidemiology, and genetics, and four working groups have been appointed for each of the solid tumor areas studied by the CALGB.

The CALGB has restructured the membership of the Pathology Committee, which will consist of Dr. Maurice Barcos as Chair, Dr. Richard Brunning as Vice-Chair for Hematopathology, and Dr. Carolyn Compton as Vice-Chair for Surgical Pathology. Dr. Schilsky also reminded the membership that Dr. James Vardiman, at the University of Chicago, is the cadre leader for leukemia and that his lab has taken over the central morphology review of leukemia and myelodysplasia specimens; all specimens for histologic review should now be sent to the University of Chicago.

Dr. Schilsky announced the formation of the Conflict of Interest Committee, which will review conflict of interest disclosure forms at each Group Meeting and recommend any necessary action to the Executive Committee.

Dr. Schilsky commented that the Central Office has received inquiries from investigators at non-CALGB institutions who want to become CALGB investigators. He then addressed how investigators become CALGB investigators: An individual's institutional PI must submit the person's name and credentials to the Central Office. Please remember that a CALGB institution can only participate in one multimodality cooperative group. For example, if an institution is a member of the

CALGB, it cannot be a SWOG or ECOG member. It can, however, be a member of multiple specialty groups—such as RTOG or GOG and one multimodality group.

Some individuals act as consultants to the CALGB in a variety of ways, e.g., Patient Advocates. The Executive Committee has adopted the position that patient advocates should be encouraged to participate in the CALGB. Each Disease and Modality Committee will be asked to appoint at least one patient advocate.

Finally, Dr. Schilsky discussed the CALGB Foundation, whose mission is to support the research of the CALGB. Recently, the Foundation has formed the Chairman's Club to help spearhead fundraising activities. Its members comprise the three former CALGB Group Chairs and is being led by Dr. Ross McIntyre.

Group Statistician's Remarks

Dr. Stephen George, CALGB Group Statistician, reported that one of the effects of the new Group and Core meeting cycle will be that the CALGB will produce only one large agenda book per year. The meeting cycle for next year is: a Core Meeting in March, a Group Meeting in June, and a combined Core and Group Meeting in November. A comprehensive agenda book will be produced in June, but for the November Meeting, an abbreviated book containing only schemas and accrual reports will be published.

Another point that Dr. George addressed involved some recent NCI initiatives in the area of informatics. During the past few months, the leadership at the NCI has encouraged more investigation in this area. This began as an internal initiative within the NCI to address their computing needs and quickly grew from there. One reason for the renewed interest in informatics is the recent developments in Europe and Japan toward standardization of terminology and procedures, particularly in the product licensing area. The U.S. FDA has recently joined in this effort toward international "harmonization," as it is known. In particular, three things are going to affect the CALGB—one will affect the statistical center, and the others will affect CALGB members. The changes are as follows:

- A new method of reporting data to the NCI. A single reporting mechanism will be developed to address the variety of information that the NCI collects.

- The Common Toxicity Criteria will be changed. These were last revised in 1984 to set a standard for the Cooperative Groups to report toxicities to the NCI in a common, consistent way. Work is under way to develop a new toxicity criteria reporting mechanism to maintain reporting consistency.
- The adverse events reporting mechanism will be overhauled. Plans call for streamlining the reporting of adverse events.

The last point Dr. George addressed was the long-term follow up of patients, which is done in all Phase III treatment studies. He commented that the Group needs to have long-term follow up information of all patients. Confusion has occurred over some of the CALGB's procedures. He stressed that the Group is not interested just in the survival of long-term patients, but that it also needs to know the primary end points of the study for *all* patients, even if for some reason they didn't receive the protocol-specified treatment.

Appointments

Jeffrey Sosman, M.D., is PI at the University of Illinois at Chicago.

Stephen Seagren, M.D., replaces Mark Green, M.D., as PI at the University of California at San Diego.

Hyman Muss, M.D., is PI at the Vermont Cancer Center

Michael Caligiuri, M.D., Chair of the AIDS Malignancies Working Group; Lawrence Kaplan, M.D., Vice-Chair.

Hyman Muss, M.D., Vice-Chair for the Breast Committee.

Thomas Smith, M.D., Vice-Chair for the Clinical Economics Committee.

Mark Ratain, M.D., Chair for the Conflict of Interest Committee.

Andrew Carroll, Ph.D., Vice-Chair for Cytogenetics, Correlative Sciences—Leukemia/Lymphoma Committee.

Daniel Hayes, M.D., Chair for the Solid Tumor Correlative Sciences Committee; Lynn Dressler, M.A., Vice-Chair.

Neal Meropol, M.D., Vice-Chair for the PET Committee.

Everett Vokes, M.D., Vice-Chair for the Respiratory Committee.

PLENARY SESSION HIGHLIGHTS

Clinical Economics

Jane Weeks, M.D., Chair of the Clinical Economics Committee, addressed the Scientific Session of the Plenary Session and provided an overview of economic analyses in clinical trials and described a current study that the Committee is conducting. Dr. Weeks presented the common dilemma faced by physicians who must justify using a promising but costly drug whose benefits have yet to be determined. Questions facing the physician are: who should get the drug; should it be restricted to certain types of patients or certain regimens; what budget should provide the additional money needed to pay for the drug; and should other drugs be cut in order to pay for the new drug? With the current climate of limited resources, which necessitates making hard choices, economic analyses can be a great help in making these choices.

Essentially, all economic analyses look at how much something costs and what one gets for the money. There are many ways to measure benefits of health care intervention. One way is in dollars, which places a price tag on improvement in health and, ultimately, on years of life saved. Another is to determine what the benefits of a treatment are in terms of units of medical effect, such as millimeters of mercury by which a patient's blood pressure has dropped.

In clinical oncology, however, it is less useful to utilize the aforementioned methods, since much of what is being evaluated is not years of life gained. Palliative therapy for example, may improve the quality of life dramatically without lengthening it.

To take that into account, it is beneficial to use quality adjusted life years (QALYs) as a measure of benefit, which take into account both the length and quality of life. To do that, the quality of life is measured in "utilities" on a scale of 0 - 1, where 0 represents death and 1 represents perfect health. This differs from other measures of quality of life in that it reflects how a patient values his state of health rather than just describing it.

Cost is often quite difficult to measure, because other components figure into out-of-pocket costs. We tend to think of direct medical costs first—hospital bill, drug bill, doctor's fee, etc. But there are nonmedical costs, too, such as if somebody must hire a babysitter when they go to the doctor. There are also indirect morbidity and mortality costs. A key component here is lost wages. If a patient is being treated and not working, he's losing wages. There are also intangible costs for pain and suffering, which are not typically measured in dollar terms but are taken into account in a cost-utility analysis.

Even direct medical costs need careful scrutiny. Several components figure—the simplest and most obvious being the cost of the intervention itself. In addition, one must take into account the cost of care resulting from the side effects, as well as costs incurred due to medical care because patients live longer. If a patient is cured of his Hodgkin's disease in his 20s and then suffers a stroke when he's 75, the cost incurred by the stroke gets charged against the Hodgkin's disease therapy.

In clinical cancer therapies, an investigator counts the number of hospital days experienced by patients in both study arms of a trial, and when the trial is completed, converts the resources to the cost. Ideally the paths of care compared should be as similar to standard clinical care as possible. The data at the end of the trial will estimate the ratio of the incremental costs of the more expensive treatment to its incremental benefit measured in terms of life saved or quality adjusted years of life saved.

For example, CALGB 9481 is a Phase III study comparing hepatic artery infusion vs. systemic chemotherapy in patients with colon cancer metastatic to the liver. The primary endpoint is survival, but there are a number of secondary endpoints, including toxicity, failure-free survival, response, quality of life, cost, and cost effectiveness. The rationale for this trial was that the response rates would be better and survival a bit longer for patients receiving the hepatic artery infusion, but the question was at what cost to the patient in terms of toxicity and at what cost to society in terms of actual dollars.

The strategy for estimating costs for

this trial was similar to those in which cost effectiveness analyses are done. Resource utilization data will be collected for all patients in the trial, along with billing data for patients at representative institutions, to determine the prices for the resources. Once the trial is over, investigators will analyze the data from the collection sites. The cost of treatment, e.g., days spent in the hospital or ICU and the average cost per day of those factors, will be evaluated for both arms. Finally, the cost of treatment in Arm A minus the cost of treatment in Arm B will be divided by the clinical data, e.g., survival in Arm A minus Arm B, to produce a cost-effectiveness ratio.

These data will then be compared with societal norms. If the survival advantage is substantial enough to offset the cost, it would help investigators in recommending that hepatic artery infusion therapy be adopted as standard practice.

These types of analyses help in making tough economic decisions by providing more tools to make the choices. While it doesn't make *making* the choices any more pleasant, it provides information necessary to function in today's world.

Melanoma

While the CALGB does not study melanoma, many of the Group's investigators see these patients at their institutions, and there are many important and exciting developments happening in the study of melanoma. Dr. John Kirkwood, from the University of Pittsburgh, spoke to the Plenary Session audience on current studies and treatment for melanoma.

Melanoma has been experiencing an epidemic rise in its incidence worldwide and is the leading cause of cancer death in women 25 to 30 years of age. By the year 2000, it is estimated that 1 in 75 people will develop melanoma. Twenty to thirty years ago, the incidence was 1 in 1500.

The charge for medical oncologists is formidable as the disease has had a standard single therapy, dacarbazine, which has been the agent used for the past 30 years. Agents that are being investigated by ECOG are the role of

1996 FALL GROUP MEETING

adding tamoxifen to chemotherapy and combinations of interferons and interleukens. As reported in the *New England Journal of Medicine*, the addition of tamoxifen showed a survival advantage in a small study, and data from a small South African trial of interferon suggested a similar advantage for survival in patients treated with interferon plus dacarbazine over dacarbazine alone.

Six years ago, ECOG studied dacarbazine vs. dacarbazine with interferon vs. dacarbazine with tamoxifen vs. all three of these agents. Analysis revealed that there was no difference in complete or partial responses for any of these combinations. Overall conclusions presented at ASCO show no difference for any of the four arms in time to failure or for overall survival. More significant may be the combination of interleukin 2 and interferon alpha.

Because there is no advantage to combinations, a variety of biological approaches and single-agent chemotherapeutic approaches will continue to be studied, including multi-peptide and ganglioside vaccine therapy. In late 1996 or early 1997, ECOG plans to embark on a multi-peptide vaccine trial. Additionally, ECOG, SWOG, and MDACC are testing gangliosides in an Intergroup trial, E1694.

In other trials—ECOG 1684, as well as ECOG 1690, an Intergroup trial in which the CALGB participated—high-doses of interferon alpha given at or close to maximum tolerable dose for one year were tested. The study showed a statistically significant improvement of survival and relapse-free survival for patients receiving high-dose interferon. This improvement was the first to have a statistically significant impact upon survival for any therapy tested in the cooperative group setting.

CALGB Foundation Raffle

Brenda Shank, M.D., from Mount Sinai Hospital, was the winner of the fund-raising raffle, which was held during the Saturday evening reception at the Fall Group Meeting. The raffle was held in order to help support the CALGB Foundation. The prize was a weekend for two in Las Vegas.

Informed Consent Research

At the Fall Group Meeting, Christopher Daugherty, M.D., from the Section of Hematology/Oncology and the MacLean Center for Clinical Medical Ethics at the University of Chicago, provided a background and history of informed consent in research and presented some relevant results of selected studies on informed consent that have been conducted in the last 20 years. He then spoke about a study conducted at the University of Chicago on the informed consent process.

A definition of informed consent in clinical research is variable, but generally speaking it is viewed as a process of communication between the patient/subject and the clinician/investigator regarding investigational or experimental treatment. Included in informed consent is specific disclosure of the risks and benefits of treatment, the unproven nature of the research, and the alternatives other than participating in the research studies. Additionally, the patient is informed of his or her freedom to withdraw from the study and that doing so will not have a detrimental effect on the patient's continued access to health care.

Generally speaking, informed consent in clinical and therapeutic research is a concept of the second half of the 20th Century. This has been shaped as much by social forces as by medical factors, particularly litigation concerns and evolving policies of the federal government. Informed consent is now most commonly viewed as a means of protecting research subjects from potential harm.

The history of the term informed consent can be traced to the Nuremberg Code of 1947, which was written as a response to crimes against humanity and which was specifically written to protect healthy volunteers in nontherapeutic human subject research. It had little impact, however, on the practice of clinical or therapeutic research at the time of its writing and does not specifically mention "informed consent." Of particular interest is the release last year of the report of the advisory committee on human radiation experiments and the making public of a little-known 1947 letter written to an investigator from the general manager of the newly formed Atomic Energy Commission (AEC). The letter was written in direct response to an investigative request to allow the classification of data from government-sponsored radiation research

so that they could be reported and published. The AEC clearly had concerns over potential litigation problems regarding cancer patients who had been used as the subjects of research without documentation and consent. There were also concerns about the public's general perception of radiation-related research. Thus the general manager stated that the policies at the AEC prevented data classification and prevented publication without clear written documentation of what he called "informed consent" of the patient subjects.

Probably the earliest recognized instances of written informed consent forms began with army physician Walter Reed's yellow fever studies of the early 1900s involving volunteer soldiers. Forms used in therapeutic research were routinely used as a policy by 1953 at the NIH Clinical Center. Approximately a decade later the thalidomide tragedy resulted in the Drug Amendments Act of 1962, which required that subjects be informed of the experimental nature of a drug. In 1966, Dr. Henry K. Beecher reported in the *New England Journal of Medicine* what he viewed as clear violations of the ethical principles of informed consent, and this had a significant impact on subsequent clinical research practice. Finally, the disclosure in 1972 of the Tuskegee syphilis studies equally affected regulatory requirements and consent and led to the formation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in the mid-1970s, which studied human subject research and related ethical issues. The commission's recommendations led to the formalized IRB scrutiny and oversight to which we are all accustomed.

A number of studies have been conducted to measure the outcomes of the consent process. One of the earliest studies on informed consent took place in 1978 and was a comprehensive study of IRBs and consent forms. It included 61 institutions, more than 2,000 investigators, and more than 1,000 research subjects. The study's authors concluded that it was questionable whether subjects found the consent form to be useful and noted that the forms were unreadable. Additionally, there appeared to be no impact of IRB review on readability or the utility of the

1996 FALL GROUP MEETING

consent form. Although disappointing, these conclusions were no more surprising than they are today. They were at least coming at a time when formal and widespread enforcement of regulatory policy had only relatively recently begun, thus there was reason to hope for improvement.

A study that dealt exclusively with informed consent in cancer care was published in a 1979 issue of *Cancer*. The study, conducted by Dr. Muss and colleagues, was one of the first to study informed consent using written consent forms. The study surveyed 100 breast cancer patients after they had given consent to adjuvant chemotherapy. The authors' conclusions were that although all of the regulatory requirements had been met, the use of written documents had little impact on patient knowledge.

A 1986 study evaluated a randomized comparison of two different consent procedures: a written form or allowing the physician to use his or her discretion in discussing the elements of consent according to their own or the patient's priorities. The survey was conducted at the time of consent to therapy and then three or four weeks later and measured the impact of the two consent procedures on patient understanding, anxiety levels, and the physician/patient relationship. Findings indicated that total disclosure appeared to lead to better patient understanding on the risks and nature of the research but also seemed to produce an increase in patient anxiety and a decrease in willingness to participate in the study. These differences, however, were not seen at the follow-up survey. There seemed to be no significant positive or negative impacts upon the physician/patient relationship with the use of total disclosure.

Little has changed in the '90s, with consent forms still unreadable and questions remaining about their value in the consent process. We've all asked ourselves if these forms matter and what purpose they serve. What we should do is ask ourselves what is happening to the consent process itself and whether or not the attention directed to the forms draws attention away from what might otherwise be a more meaningful consent process.

A study that is being conducted at the University of Chicago examines the process of clinical trials and is studying the ethical dilemmas in clinical cancer

research. This study examines the participating patients' and physicians' motivations and perceptions toward investigational therapies—their expectations and goals regarding the clinical process and, perhaps most importantly, their comprehension and understanding of the nature of therapeutic clinical research. Approximately 150 cancer patients participating in Phase I trials have been asked specific questions about informed consent. The vast majority of patients said that they were aware that they were participating in a research trial, that the possible risks and side effects of participation had been disclosed in the consent process, that the possible benefits had been disclosed, and that their freedom to withdraw had been disclosed. The vast majority of patients cited the possibility of therapeutic benefits as the reason for participating in the trial. A small minority said their motivation to participate stemmed either from advice from a physician or because of direct family pressure. None mentioned altruistic reasons.

The University of Chicago study indicated that more than half of the patients believed the research purpose of these trials was either to determine tumor response or therapeutic benefit. Approximately one third of the patients thought the purpose of a Phase I trial was a method to determine dose, perform dose escalation, or determine tolerability. Fifteen percent said they didn't know the purpose of a Phase I trial. Physicians were also asked about their patients' perceptions and level of informed consent, and patients were queried about their perceptions on clinical trial participation. Generally, the majority of patients viewed their level of informed consent as excellent, but only a small minority of physicians shared this view.

The regulatory process of clinical research, including the use of written consent forms, is important to prevent the potential for abuse. It appears, however, that consent forms themselves have had little direct effect on the quality of the consent process—remaining unreadable and of questionable clinical utility. If improvement in the informed consent process is to be performed from a policy standpoint, this improvement should not come through increased regulatory requirements. Rather, it should come from increased awareness of the ethical obligations that clinical investigators have

and of patients' motivations and expectations toward investigational therapies. Research should continue on the practices of informed consent and on the chance for investigators to develop innovative methodologies for consent.

Genetic Testing and Cancer

Eric Kodish, M.D., spoke at the Fall Group Seminar on Ethics in Oncology and Clinical Research on the ethical and societal implications of genetic testing for cancer. He stated that as the human genome initiative moves forward, oncologists and their patients face the prospect of a mixed blessing and a curse. The ability to predict with near certainty a patient's risk for cancer before any clinical manifestation appears brings about a new role for genetics in the world of oncology. Up until this decade, the utility of genetics for the oncologist had been to clarify diagnosis and, to some extent, to establish a prognosis. Along the way, genetics has given us a better understanding of the pathophysiology and the underlying mechanism of human neoplasia. We have come to foster a great hope for genetic therapy for cancer, but now genetic testing for cancer risk has arrived in the realm of predictive science, and in this sense, testing healthy patients for germline mutations that predict a future malignancy makes it the genetic equivalent of the crystal ball to predict the future.

This raises some important questions on the risks and benefits of cancer genetics testing and informed consent. The questions are: Where are we in the evolution of our scientific and clinical understanding of a particular cancer gene? and what good is our knowledge of the test results?

Cancer is a rapidly changing field and cancer genetics is even more so. Because genetic testing for cancer by its very nature is such a revolutionary concept, we have to recognize its potential for misapplications. It is our responsibility to make recommendations to our patients and our subjects based upon the data and not on speculation and to be cautious about the special benefits and the potential risks until

more definitive data are available.

Informed consent can be different in a clinical setting than it might be in a research setting, and certainly in the presymptomatic or screening setting we might need a different way of doing informed consent.

Benefits of a Positive Test

All of the benefits are fairly speculative. A positive test may prove medically beneficial if it leads to early detection or prophylactic therapy that is effective and if it provides control or knowledge to the person who undergoes testing. The test specifically assists in making reproductive decisions. Longitudinal studies are needed to determine if there will be decreased morbidity or mortality from genetic testing for cancer risk. These data are missing even for radical measures such as bilateral mastectomy or oophorectomy in women who may be positive for BRCA1.

Benefits of a Negative Test

A negative test may provide freedom from anxiety, improve insurability of the person undergoing the test, avoid unnecessary prophylactic surgery, and make reproductive decisions easier. Currently, reproductive decisions are probably the most valuable, and most under-appreciated, benefit of genetic testing.

Risks of a Positive Test

A positive test may cause feelings of anxiety, helplessness, depression, and create the potential for genetic discrimination. It's important to note that there is no risk medically, per se, of a negative test.

Economic concerns—the difficulty in finding life, health, or disability insurance in our present system—are very real concerns with a positive test. The confidentiality of a genetic test needs to be maintained to protect individuals from employers' and insurers' scrutiny. While there is much legislative activity revolving around the issue of confidentiality of genetic test results, there is fierce opposition to this from many quarters. Rapid and profound changes in our health-care system, for example, the merging of the identities of health-care providers and health-care insurers, are going to make protecting the privacy of these test results exceedingly difficult. As health-care professionals, we need to be aware that there will be pressures from many different quarters to disclose these test

results, and they need to be resisted.

Risks of a Negative Test

A negative test may result in a false sense of security. People will often want to quit performing their normal cancer control measures, such as breast self-examination or fecal occult blood testing. Additionally, some genetic counselors have reported some sense of survivor guilt from having a negative test.

All of the aforementioned risks and benefits apply to a single individual. We need to understand that informed consent is designed for a single individual based on the traditional concept of autonomy. In reality, individuals live in a context of families, and there, decision making is not truly autonomous or independent. The results of a cancer gene test have potential implication for family members, since if one individual in a family tests positive, others might also test positive. Because this risk is inherited, parents, siblings, children, and others in the family might have an interest in knowing the results of the test. The compelling argument to disclose to family members has to be balanced against the traditional commitment to respect the privacy and confidentiality of the individual who is being tested.

It is interesting to consider testing for genetic cancer risk in the context of a continuum, with no abrupt transition between research and the practice of medicine. It helps if we compare two recently published statements that illustrate the issues. In 1994, a statement on the use of DNA testing for presymptomatic identification of cancer risk appeared the Human Genome Project and was published in the *Journal of the American Medical Association*. It called for attention to the following issues: to define the patient's frequency and associated risk; to look at technical and laboratory issues; to look at the effect of intervention on morbidity and mortality; and to avoid genetic discrimination. This group said that until more information was available to address these critical issues, it was premature to offer DNA screening for cancer predisposition outside the carefully monitored research environment.

Two years later, ASCO issued its statement on genetic testing for cancer susceptibility in which it suggested that genetic testing should be made available to selected patients as part of the preventive oncologic care of families in conjunction with appropriate education, informed consent, and supportive

counseling. The picture had changed, taking the genetic testing for cancer risk from the realm of research to the realm of clinical practice. The ASCO statement sets up practice guidelines that state real indications for genetic testing in cancer predisposition, i.e., if the person has a strong family history of cancer or very early age onset; that the test be adequately interpreted; and that the result would influence the medical management of the patient or family members. The statement also provides guidelines on the necessary elements of consent and also calls for further research on these issues.

Perhaps the most important contribution of the ASCO guidelines is that it develops a taxonomy of cancer gene tests. The three groups in this taxonomy are:

1. Tests for families with well-defined syndromes where either a positive or negative test would result in a change in medical care.
2. Tests for hereditary syndromes probably linked to known cancer genes for which medical benefit is presumed but not established.
3. Tests for individuals without family history of cancer, for syndromes with germline mutations in small numbers, or where medical benefit is not established.

The ASCO guidelines suggest that oncologists offer genetic testing only for the first two categories and that testing for group three is considered research with unknown clinical applications.

What are some of the changes that have taken place in the last two years? Advances in science allow for gene sequencing that obviates the need for expensive and complex linkage analysis. With more capital investment, there is an increased commercial pressure to produce returns on the investment. More media attention has increased patients' demands for access to testing. Clinical studies of women with breast cancer have indicated a high level of interest in testing. Many times, though, a woman's interest in being tested often wanes when she finds out the insurance issues. Nevertheless, it is still safe to say that there is a heavy demand for cancer gene testing. Currently, there are at least three biotechnology companies that are marketing clinical tests for cancer predisposition genes.

A simple blood test to predict susceptibility to a serious disease can be attractive to doctors, patients, insurers, and to companies who market these tests. In the final analysis, however, it is the responsibility of the health-care professional to utilize lab testing in a prudent manner and to order only tests that are indicated.

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