

Clinical Trials

Ian Magrath
President of INCTR

Melissa Adde
Coordinator of INCTR's Strategy Group, Ethical Committee
Director of INCTR's Clinical Trials Office

Objective Tools for Evaluation

- Diagnostic tests
- Screening modalities
- Prevention strategies
- Therapeutic interventions

Multidisciplinary Cancer Management Course

Importance of Clinical Trials

- Essentially all advances in cancer diagnosis and treatment have resulted from clinical trials
- Patients have opportunity to receive new therapies that may
 - Be better than the standard of care
 - Contribute to new knowledge that will benefit other patients
- Instrument to improve the quality of care, by standardizing treatment protocols

Participation

- Less than 3% of adult patients in the United States participate in cancer clinical trials
- Clinical trials provide new, potentially better options compared against the best current standard of care

Participation (cont.)

- Rigorously reviewed protocols maximize the safety for patients
- Informed consent procedure ensures patient and physician education regarding current options in the treatment of the disease

Multidisciplinary Cancer Management Course

Scientific Issues

- Hypothesis: Is the question addressed by the study important?
- Study population: What are the eligibility criteria for subject inclusion and exclusion?
 - Disease type and stage
 - Functional performance status
 - Number and type of prior therapies
 - Organ function: liver, kidney, bone marrow . . .

Scientific Issues (cont.)

- Endpoints: Which parameters will be measured?
 - Remission rate, progression-free survival, overall survival
 - Quality of life, symptom control
 - Ancillary studies: blood and tissue levels of drug and target inhibition, imaging of tumor size, and metabolism
- Biostatistical considerations
 - Appropriate study design
 - Numbers and types of patients

Types of Therapeutic Clinical Trials

- **Phase I:** First study with humans
- **Phase II:** Estimates of efficacy
- **Phase III:** Randomized, standard of care comparison of two or more therapies

Multidisciplinary Cancer Management Course

Phase I Clinical Trials: Objectives

- Primary objectives
 - Evaluate safety and toxicity
 - Establish recommended dose for phase II trials
- Secondary objectives
 - Determine the metabolism and excretion of a new agent or its interaction with other drugs (pharmacokinetics)
 - Explore the effects of the new drug on molecular targets in tissues (pharmacodynamics)
 - Observe possible antitumor effects (uncommon in phase I trials)

Phase I Clinical Trials: Characteristics

- First trials of a new agent or combination
- Patients usually have advanced disease
- Wide variety of tumors types are tested
- Relatively small number of subjects (15-30)

Multidisciplinary Cancer Management Course

Phase I Clinical Trials: Limitations

- Small number of patients means that only frequently occurring toxicities are likely to be observed
- Probability of clinical benefit may be low because the first groups (cohorts) of patients are treated with low, sub-therapeutic doses
- Drugs may not be metabolized in patients with advanced disease the same way as in patients with earlier disease
- Specific studies may be required to determine safety and dosing for patients with renal or hepatic dysfunction

Phase II Clinical Trials: Objectives

- Determine antitumor activity
- Identify appropriate disease setting
- Evaluate drug effects in subsets of patients
- Delineate toxicities of treatment

Phase II Clinical Trials: Characteristics

- Usually larger than phase I trials (20-80 patients)
- May be randomized but not powered to define a new standard of care
- Tumor shrinkage is generally not sufficient to confirm a new therapy
- Usually lead to a definitive phase III trial

Multidisciplinary Cancer Management Course

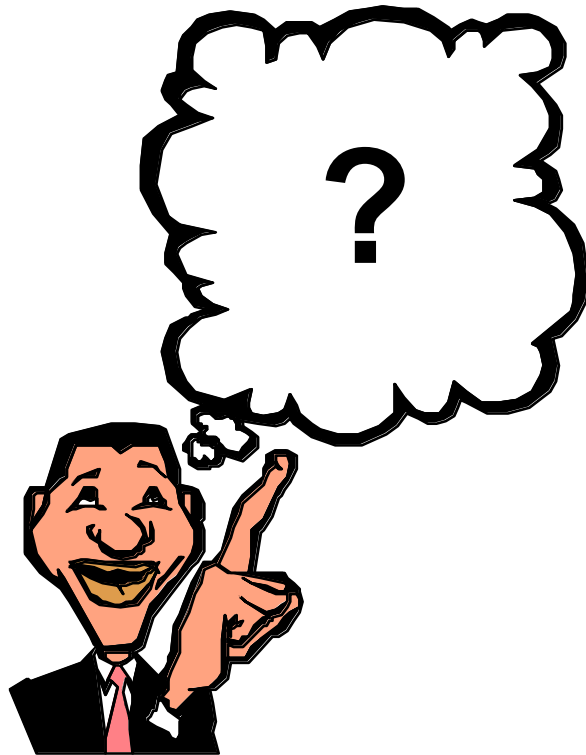
Phase III Clinical Trials: Objectives

- Designed to determine true utility
- True utility may be defined as
 - Better than “no treatment”
 - Better than a “standard” treatment
 - Equivalent to “standard” treatment but less toxic or less expensive

Phase III Clinical Trials: Characteristics

- Can be conducted with patients who have early or late disease
- Randomized to compare two or more standard and experimental regimens
- Designed to define standard of care
- Typically include large number of patients (hundreds to thousands)

Clinical Trial Design

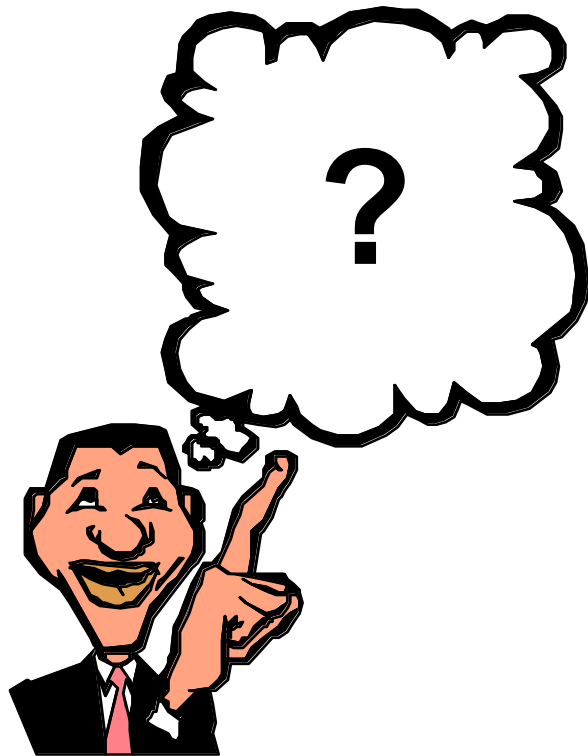


The question

- Is it relevant?
- Is it feasible?

(Can it be answered?)

Clinical Trial Design (cont.)



The question

- Is it worth it?
- What study endpoints will provide the answer?
- What else can we learn?

Clinical Trial Design (cont.)



The population

- Is it representative?
- Is it significant?
- Is it available?

The Control

- Types of controls
 - Historical
 - Pair matched
 - Contemporaneous
- Randomization
- Stratification: balancing major variables
- Placebo use and blinding

The Hypothesis

How we answer the trial question

- Null hypothesis
- Alternate hypothesis
- One-tailed and two-tailed hypotheses





The Hypothesis (cont.)

The p value represents the probability of obtaining the observed result if the null hypothesis is true.

- One-tailed alternate hypothesis → one-sided p value
- Two-tailed alternate hypothesis → two-sided p value

Multidisciplinary Cancer Management Course

Making Decisions: Traditional Hypothesis Testing

	H_0 is True	H_0 is NOT True
Accept H_0		 Type II error
Reject H_0	 Type I error	

alpha = probability of Type I error (level of significance)

beta = probability of Type II error

1-beta = power

Multidisciplinary Cancer Management Course

Hypothesis Testing and Drug Trials

Clinical Trial

Drug is useless

Drug is effective

Level of significance

Keep an effective drug

Abandon useless drug

Keep a useless drug

Abandon effective drug

Statistical Test

Null hypothesis

Alternative hypothesis

Level of significance

Correctly reject H_0

Correctly accept H_0

Type I

Type II

P Values and Confidence Intervals

- Before start of trial: specify alpha and beta errors
- After analysis of trial: summarize results with p value
- BUT... Small “p” does not always equal “Big Effect”
 - Summarize size of effect with estimate and confidence interval
- Report estimates, confidence intervals, and p values

Planning a Study: Sample Size and Power Analysis

- Sample size calculations estimate the number of patients needed to accomplish study goals
- Power analysis estimates the “power” to detect specified differences, given a particular sample size

Multidisciplinary Cancer Management Course

P Value

- Descriptive statement: How consistent or inconsistent are the observed data with what would be expected by chance? (Null hypothesis [Ho] is true)
- $P = 0.01$ means: IF Ho is true, 1 time in 100 we would get something like this OR something even more inconsistent with Ho. Thus, there is a 99% chance that the null hypothesis is false.

Summary Statistics and Confidence Intervals

- **Relative Risk (RR)** is a point estimate of the effect of the experimental treatment
- **Confidence interval (CI)** gives a range of population RRs that are consistent with the sample data

Error and Sample Size

Type I error (alpha): Incorrect **rejection** of the null hypothesis

- Poor design
- Inappropriate population
- Random chance

Error and Sample Size (cont.)

Type II error (beta): Incorrect **acceptance** of the null hypothesis

- Small but real difference between groups
- Too few patients and “events” for comparison

Power

- **Power (1-beta)** is the chance a study has of detecting a difference between treatment arms ... if such a difference exists
- The greater the power, the larger the study population required for a given number of events and a given difference between groups

Alpha and Beta Levels

- alpha is the level of significance
- Minimizing alpha means having confidence that a treatment difference truly exists
- Minimizing beta means having confidence that you will **correctly** conclude that no difference exists

Alpha and Beta Levels (cont.)

Suppose you want to compare the response rates of two treatments. You expect your new treatment to have a response rate of 35% and the current standard, to be used in the control group, has a response rate of 15%. You want to test the difference at the $\alpha = 5\%$ level of significance, and you want the study to have 80% power (20% beta error) to detect this difference.

- How many patients do you need to study?

Multidisciplinary Cancer Management Course

Alpha and Beta Levels (cont.)

Sample Size per group for comparing two proportions												
Min of P1 and P2	Alpha	Beta	Expected Difference between P1 and P2									
			0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
0.05	0.10	0.20	342	110	59	38	27	21	17	13	11	9
	0.10	0.10	473	152	81	53	38	29	22	18	15	12
	0.05	0.20	434	140	75	49	35	27	21	17	14	12
0.10	0.05	0.10	581	187	100	65	46	35	28	22	19	15
	0.10	0.20	540	157	78	48	33	25	19	15	12	10
	0.10	0.10	747	216	108	67	46	34	26	21	17	14
0.15	0.05	0.20	686	199	100	62	43	31	24	19	16	13
	0.05	0.10	917	266	133	82	57	42	32	25	21	17
	0.10	0.20	713	197	95	57	38	28	21	17	13	11
0.20	0.10	0.10	987	272	131	78	53	38	29	22	18	14
	0.05	0.20	905	250	120	72	49	35	27	21	17	14
	0.05	0.10	1212	331	161	96	65	47	36	28	22	18
0.25	0.10	0.20	861	231	109	64	42	30	23	17	14	11
	0.10	0.10	1193	319	150	88	58	41	31	24	19	15
	0.05	0.20	1094	293	138	81	54	38	29	22	18	14
0.30	0.05	0.10	1464	392	184	108	72	51	38	29	23	19
	0.10	0.20	985	259	120	69	45	32	24	18	14	11
	0.10	0.10	1364	358	165	96	62	44	32	25	19	15
0.35	0.05	0.20	1251	328	152	88	58	41	30	23	18	14
	0.05	0.10	1674	439	203	117	77	54	40	30	24	19
	0.10	0.20	1084	280	128	73	47	33	24	18	14	11
0.40	0.10	0.10	1501	388	177	101	65	45	33	25	19	15
	0.05	0.20	1376	356	162	93	60	42	31	23	18	14
	0.05	0.10	1842	476	217	124	80	56	41	31	24	19

P1 = 0.35 vs. P2 = 0.15
 $\alpha = 5\%$
Power = 80%

Reprinted with permission from Hulley SB, Cummings SR. *Designing Clinical Research: An Epidemiological Approach*. Baltimore, Md: Williams & Wilkins, 1988.

Alpha and Beta Levels (cont.)

- Having a small beta is important in “equivalency” trials
- The smaller the alpha and beta, the larger the sample size will be

Interactions

- Unappreciated interactions may occur
- Global tests for interactions should be used
- Individual subset analyses may be utilized
- Beware of the “observer effect” in subset analyses
- Conclusions from subset analyses are always suspect

Comparisons of Groups

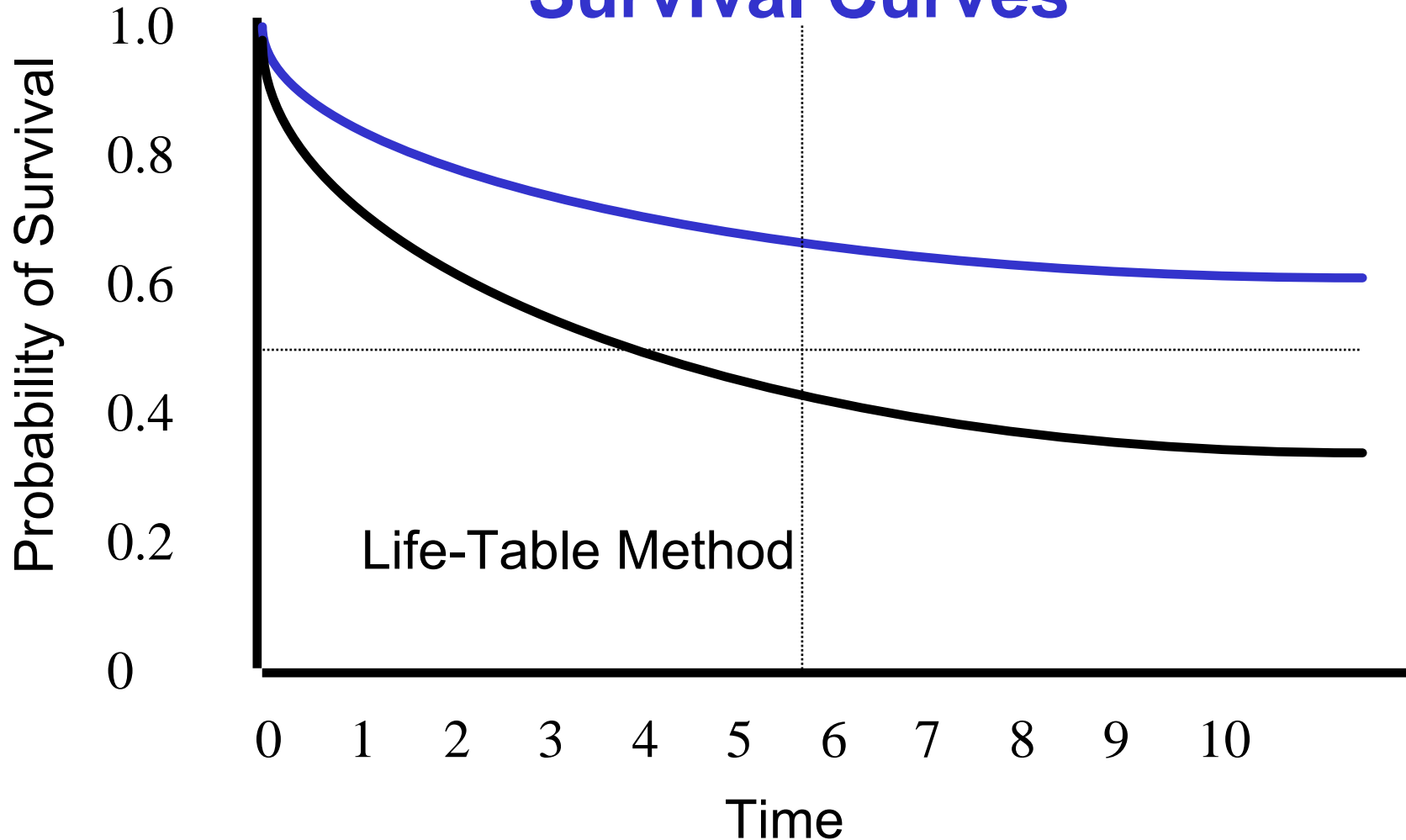
- Comparison of means
 - t test: mean values of a continuous outcome variable
 - z statistic: compares the proportion of participants with different outcomes
 - Confidence intervals
 - Relative risk
- Continuous analyses of failure (survival analyses)

Survival Analyses

- Survival functions are plotted as proportion surviving against time from randomization
- Survival functions may be estimated using
 - Life table method
 - Product limit method

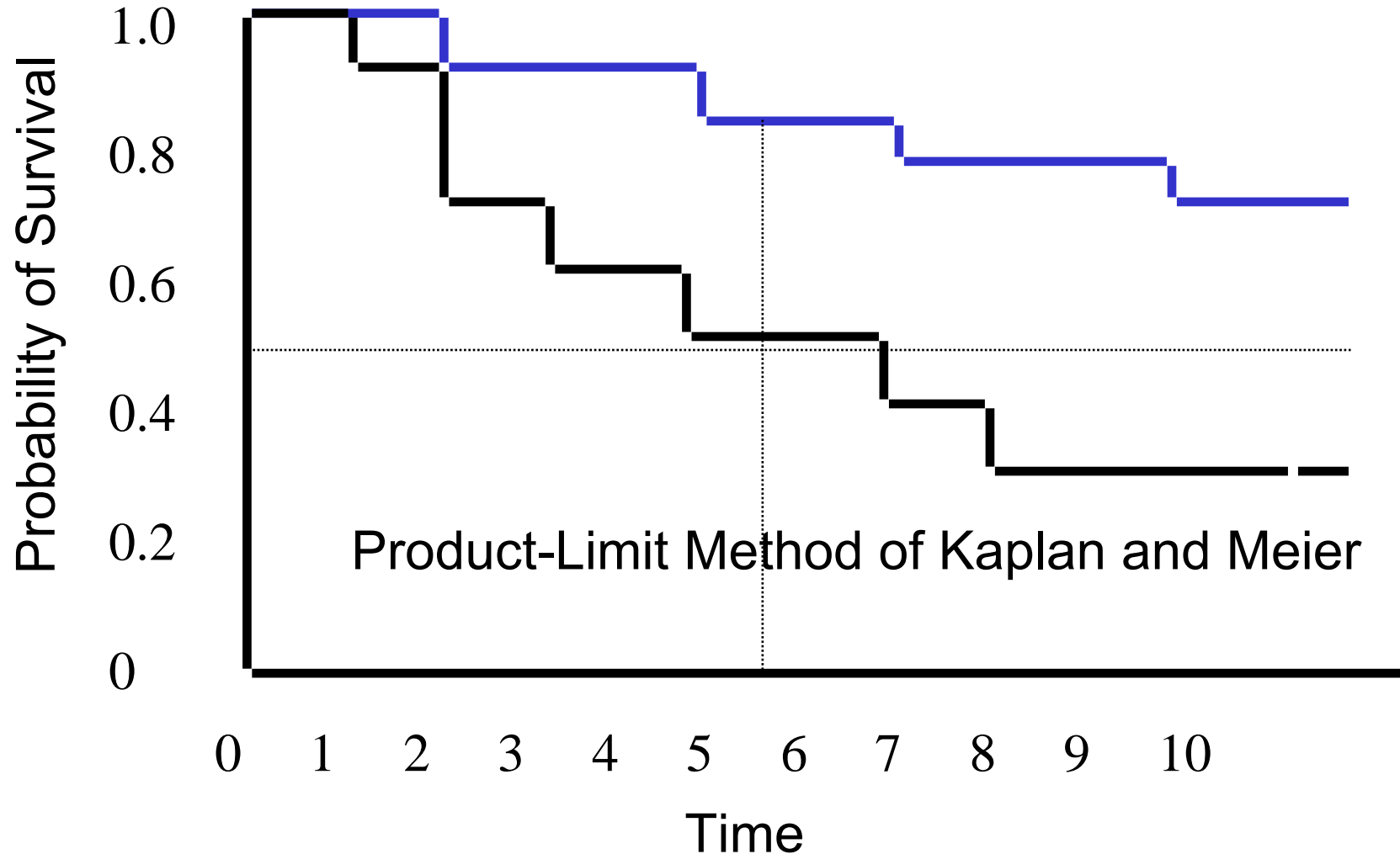
Multidisciplinary Cancer Management Course

Survival Curves



Multidisciplinary Cancer Management Course

Survival Curves



Reporting Results

- State quality control methods
- Account for all patients
- Make sure the number of unevaluable patients is less than 15%
- Compare endpoints for eligible population
- Publish confidence intervals for negative results

Reporting Results (cont.)

- Explain alterations in sample size
- Do not make claims for efficacy in nonrandomized phase II trials
- Describe how the study patients reflect the target population
- Use caution in reporting subset analyses
- Describe statistical methods in sufficient detail as to allow reproduction

Data Management

- Request only relevant data
- Design easy-to-use data forms
- Minimize data delinquency
- Perform appropriate audits
- Minimize edits

Multidisciplinary Cancer Management Course

Ethical Issues

- Make the patient a participant
- Obtain written informed consent
 - Provide detailed information
 - Check the patient's comprehension
 - Stress the voluntary nature of participation
 - Allow time for the patient's decision process

Ethical Issues (cont.)

Protection of human subjects in research

- Protocol review by independent ethics committee
- Written informed consent process
- Reporting of serious adverse events
- Data and safety monitoring

Ethical Issues (cont.)

Conflicts of interest

- Investigators should disclose potential conflicts in the consent form and protocol application
 - Sponsorship of the study by a company
 - Participation in advisory boards or speaking honoraria
- Physicians with a major conflict of interest (stock ownership, substantial honoraria) should not directly participate as investigators for those companies

Ethical Issues (cont.)

Investigator responsibilities

- Scrupulous adherence to the protocol
- No toleration of dishonesty
- Disclosure of potential conflicts of interest
- Accurate and timely data entry
- Prompt reporting of adverse events

Ethical Issues (cont.)

Investigator and sponsor responsibilities

- Make changes to the protocol only with formal protocol amendments and with approval from Ethics Committee
- Conduct impartial data reviews with interim analyses
- Publish results in a timely manner

Summary

- Clinical trials have led to essentially all advances in cancer diagnosis and treatment
- Determining a sound scientific question, establishing appropriate endpoints, and selecting the study population are key elements in clinical trial design
- Statistical considerations include sample size, power, and alpha and beta errors

Summary (cont.)

- A well-planned protocol document is critical for conducting a clinical trial, and strict adherence to the document is essential
- Ethical issues in clinical trials involve the protection of participants, disclosure of conflicts of interest, accurate and timely reporting of results, and prompt reporting of adverse events

Clinical Trials in Cancer

“One must attend in medical practice not primarily to plausible theories, but to experience combined with reason”

- Hippocrates