Contents

1. Introduction 1

References

2. Quantitation 4

General principles / Assessment of tumor shrinkage / Measurable versus evaluable disease / Measurement of measurable disease / Physical examination of palpable masses / Radiographic methods of measuring disease / Radioisotopic scanning / Definition of response / General features of response evaluation / Problems with measurement in special situations / Meaning of response categories / Disease progression / Local versus systemic recurrence / Measuring duration of objective benefit / Staging /Will Rogers phenomenon / Conclusions / References

3. Treatment toxicity and quality of life 23

Toxicity / Anticipating important toxicities / Quantitation of toxicity / Initial screening / Recording anticipated events / Unanticipated events and toxicity / Accurate attribution of adverse events / Analysis of drug toxicity data / Chronic and late toxicities / Quality of life / Self-report questionnaires / Specialized instruments / References

4. Phase I trials 41

Selecting drugs for clinical testing / Selecting patients for trial / Safe starting dose / Drug schedules / Dose escalation / Terminating the study / MTD is a relative concept / Phase I studies in children / Antitumor activity / Dilemmas in Phase I / References

5. Phase II trials 60

Determining tumor types for study / Selecting patients for trial / Previously treated patients / Drug schedules / Determining the level of drug activity of interest / Determining activity of drugs / Reliability of Phase II trials / Randomized Phase II trials / Crossover design for Phase II studies /Survival as an endpoint in Phase II studies / Phase II studies in children / Conclusions / Appendices / References

6. Design of Phase III studies 77

Research questions that can be addressed by comparative clinical trials / Selecting patients for study / Generalizability of the data / Appropriate controls / Performing randomization / Unbalanced randomization / Designs involving common controls / Prognostic factors and stratification / Determining endpoints / Sample size / Sequential design / Factorial design / Crossover design / Assuring adequate patient accrual / Appendices / References

7. Analysis of comparative trials 104

Comparison of proportions responding on each arm of a study / Construction of survival curves / Comparison of survival curves / Sources of bias in the analysis of survival curve data / Exclusions, losses and removal of patients / Interim analyses / Treatment–covariate interactions / Pooling data / Appendices / References

8. Combination chemotherapy 129

Scientific considerations / Drug selection / Dose selection / Schedule selection / Optimal duration of therapy / Role of theoretical models / Practical issues in clinical trials methodology / References

9. Combined modality therapy 150

Definitions / Goals and endpoints / Hypotheses and the design of regimens / Selection of patients / Current issues / Design of regimens / Subgroup-specific effects / Long-term follow-up and reporting of results / References

10. Biologic response modifiers 171

Definition of terms / Problems in the study of BRMs / Design of trials / Antibody therapy / Maturational agents /Combination therapy with BRMs and other modalities / Conclusions / References

11. Elements of a protocol 191

Title page and table of contents / Aims or objectives of the study / Background and rationale / Patient eligibility / Treatment program including schematic diagram / Agent information / Dosage modification and procedures to be followed in event of toxicity / Required laboratory and clinical data / Criteria for evaluating the effect of treatment / Criteria for removing a patient from study / Statistical considerations / References / Forms / References

12. Protection of human subjects 206

Background / Institutional review / Informed consent / Elements of informed consent / Special considerations regarding children / Assessment of patients' reactions / Assessment of physicians' reactions / Ethics of clinical trials / References

13. Quality control 217

Qualification of the participants in a clinical trial / Data collection and submission at the institutional level / Data management at the central office / Data analysis / Systematic variability in institutional performance / What constitutes a deviation? / Regulatory aspects / Application to single institutions / Conclusions / References

14. Reporting a trial 231

Materials and methods / Results / Discussion / Reviewing the literature / References

Subject index 239