Developing a Therapeutic Trial Protocol

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COI per FDA 21CFR54.2: None applicable to this lecture

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Learning Objectives

- Understand the elements and design of therapeutic clinical trials
- Learn how to write and get clinical trials approved and activated
- Understand the pitfalls in the conduct of trials

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Protocol Development: Outline

- **Therapeutic roles: prevention, cure, palliation.**
- **Roles of different modalities: surgery, radiation, chemotherapy, combinations.**
- **Steps in development of a therapeutic trial.**
- **Ways to speed protocol writing.**
- **Choice of primary and secondary objectives.**
- **Appropriate inclusion and exclusion criteria.**
- **The treatment and evaluation schedule.**
- **Assessment of toxicity and reporting AEs.**
- **Scheme for dose modification.**
- **Measurement of outcome: recurrence, response, or survival.**

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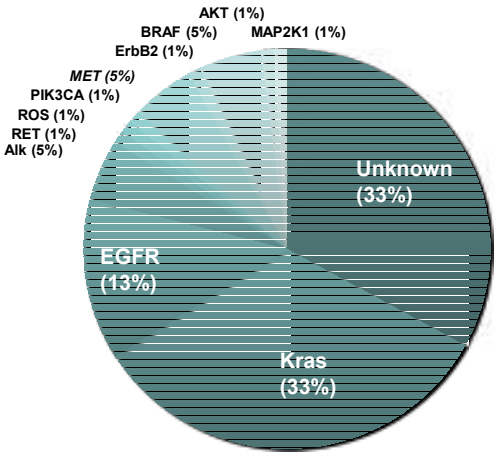
Trial Complexity: Eligibility & Screening Non-Small Cell Lung Cancer Treatment

Eligibility in 2000
- Adequate PS
- Normal routine labs

Eligibility in 2022
- Adequate PS
- Normal routine labs
- Adenocarcinoma vs. squamous cell cancers
- Prior RX e.g. platinum, targeted agents, immunotherapy
- Mutational status: EGFR, ALK, MET, KRAS etc. Immunologic markers



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Trial Complexity Increased

Early efficacy trials (phase II) in the past (~2000) required a minimum of assessment and testing:

Example

Liposomal doxorubicin trial in refractory colorectal cancer:

(Shields AF et al, Am J Clin Oncol, 2001)

- Routine blood tests: CBC, Multiphasic
- Routine CT assessment
- Drug given IV once every 3 weeks in clinic
  - No molecular markers
  - No PK blood samples
  - No biopsies

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Trial Complexity Increased: Liposomal Doxorubicin Trial in Refractory Colorectal Cancer

STUDY CALENDAR							
CYCLE	1		2		3		4
REQUIRED STUDIES	PRESTUDY	13*	21	34	42	55	63
PHYSICAL∂							
History and Physical Exam	X	X		X		X	
Weight and Performance Status		X		X		X	
Tumor Measurement	X				X		
Toxicity Notation	X	X		X		X	
LABORATORY*							
WBC, diff, platelets	X	X	X	X	X	X	X
SMA 12, lytes	X		X		X		X
CEA (q 2 treatments)	X				X		
X-RAYS AND SCANS++							
CT, MR, or PET of liver	X				X		
Other x-rays/scans for tumor measurement		X				X	
TREATMENT							
DOXIL		X	X	X		X	

2001:
Protocol 23 pages, budget $50,000 for 17 patients

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Trial Complexity Increased

Early efficacy trials now include:

Phase I trial expansion cohorts in specific diseases and targets

Phase I/II trials combining targeted agents

Randomized phase II studies

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Trial Complexity Increased

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Example

Phase I study in refractory cancer- colorectal cancer expansion cohort with phase III trial to follow.

- **Routine blood tests: CBC, Multiphasic**
- **Routine CT assessment.**
- **Drug usually taken at home with drug diary and pill counts**
- **Tumor biopsy done before and during therapy for PD**
- **Baseline ophthalmological exam, brain MRI, ECHO**
- **Multiple blood samples during treatment for PK over 8 hours**
- **Pharmacodynamic blood sampling of leukocyte mRNA marker**
- **Frequent EKGs**
- **Blood and urine samples archived**
- **Adding real time symptom monitoring by daily electronic diary**

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Trial Complexity Increased

Phase I colorectal expansion

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Table 4b: Visits in Screening and Cycle 1 for Schedule 3	Screening	Week 1				Week 2	Week 3	Week 4
	Within 14d prior to 1st dose	D1	D2[20]	D3	D5 [20]	D8[20]	D15 or 17	D24
Written Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Medical History & Prior Cancer Treatments	X							
Complete Physical Examination & ECOG[2]	X	X[28]						
Standard Clinical Neurologic Examination[2]	X							X
Visual Acuity Examination[3]	X							X
Full Ophthalmological Exam[25]	X							
Body Surface Area	X	X						
Weight	X	X				X	X	X
Symptom Directed Physical Evaluation			X		X	X	X	X
Blood Pressure, Pulse, Temperature[4]	X	X	X	X	X	X	X	X
12-lead Electrocardiogram (ECG)[5]	X	X	X			X		X
Serum Pregnancy Test (within 7 days of dosing)	X							
Urinalysis (& dipstick microscopy if clinically significant)[6]	X	X						X
Urine for Archiving[7]		X	X[7]					
Complete Serum Chemistry[8]	X	X		X	X	X	X	X
Serum Troponin Level[27]		X						X[27]
Thyroid Stimulating Hormone (TSH)[27]		X	X[28]					
Coagulation tests (PT, INR, aPTT)[10]	X	X						X[27]
CBC with Differentials[11]	X	X			X		X	X
CT or MRI Scan Tumor Measurement[12]	X							
PET-CT or PET-MRI Scan Tumor Measurement (Optional)[13]	X[13]						X[13]	
Brain MRI with contrast[14]	X							
Chest Radiograph[15]	X							
Oxygen Saturation (Pulse Oximetry)[16]	X	X			X		X	X
Transthoracic echocardiogram (cohort 2)[26]	X[26]							
[redacted] Dosing in Clinic[17]		X		X		X	X	X
Minimum clinical observation time post dose[18]		8 hr					8 hr	
PK: Serum concentration [redacted]		X[19]	X[19]	X[19]			X[19]	
PDn: Blood Pharmacodynamic Assay[19]		X[19]	X[19]	X[19]			X[19]	
Tumor Biopsy[21] (total of 2 biopsies)	X						X[21]	X[21]
Adverse Events		X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X

Table 5: For ALL Patients: Visits in Cycles 2 & 3 & For Patients who are Not Tolerating [redacted] or non-compliant[8]	Cycles 2 & 3				Final Visit
	D1	D8 or 10[11,39]	D15 or 17	D24	Within 30 (±7) days post last dose
Complete Physical Examination & ECOG					X
Weight	X		X		X
Symptom Directed Physical Evaluation	X			X	
Standard Clinical Neurologic Examination[2]				X	X
Visual Acuity Examination[3]				X	X
Blood Pressure, Pulse, Temperature[4]	X	X	X	X	X
12-lead Electrocardiogram (ECG)[5]				X	X
Oxygen Saturation (Pulse Oximetry)[16]	X	X	X	X	X
Pregnancy Test					X
Urinalysis (& microscopy if clinically significant)[6]				X[27]	X
Serum Chemistry[8,9]	X[9]	X[9]	X[9]	X[9]	X[9]
Serum Troponin Level[27]				X[27]	
Thyroid Stimulating Hormone (TSH)[27]	X[27]				X[27]
Coagulation tests (PT, INR, aPTT)[10]			X[10]		X
CBC with Differential[11]	X		X	X	X
CT or MRI Scan Tumor Measurement[12]				X[12]	
Brain MRI with contrast[14]				X[14]	
Transthoracic Echocardiogram (cohort 2)[26]				X[26]	
[redacted] Dosing in Clinic[17]	X	X	X	X	
Minimum clinical observation time post dose[18]			4 hr		
PK: Serum concentration [redacted]			X[19,27]		
PDn: Blood Pharmacodynamic Assay[19]			X[19,27]		
Adverse Events	X	X	X	X	X
Concomitant Medications	X	X	X	X	X

Protocol about 100 pages
Consent 28 pages
budget about $30,000 per patient

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Clinical Therapeutic Studies

- Most therapeutic trials involve treatment of advanced disease
  - Done with palliative intent
  - Simplest to perform
- Trials done with curative intent are generally adjuvant studies after surgery for solid tumors or chemotherapy for leukemia/lymphoma
  - Use regimens proven effective in advanced disease
  - Require large phase II and III trials
- Prevention trials may include vitamin and hormonal therapies
  - Require extremely large patient populations and years to complete

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Clinical Therapeutic Studies

- Surgery is the backbone of effective treatment for most solid tumors
  - Usually done with curative intent
- Radiation can be done with curative or palliative intent
  - Most protocols use radiation with curative intent, either as primary therapy or adjuvant treatment
- Chemotherapy trials generally use new drugs with palliative intent
  - May include single agents or complex combinations (usually the latter)
  - Successful use of new agents in the advanced setting can lead to their use earlier in therapy

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Routine Care and Trials Often Target Driven: Tumor Needed for Genomics

- Increasing need for more tumor sample for testing
- Fine needle aspirates are generally not adequate
- Full genomic panels require several good tumor cores
- Many studies need tissue for genomic testing and histology
- Clear communication with radiologists and surgeons is needed to obtain samples
- Orders for pathology need to be clear to get appropriate testing

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So you have an idea – Sources of new protocol

- Extension of pre-clinical laboratory work
- Inspired by a unique patient or series of patients
- A new imaging instrument is available
- New software or hardware have improved an older instrument
- A common problem or disease seen at your institution (listen to the questions clinicians ask)
- A device or pharmaceutical company suggests a protocol to you

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Design: The Basics

- Evaluate study protocol idea with colleagues
  - feasibility
  - coordinated with other research programs
  - adequate space, personnel availability/ commitment
- Competing protocols for patients?
- Protocol complements other studies
  - can include patients enrolled in another protocol
  - will include a similar tumor type as an ongoing protocol, but with different eligibility (esp. molecular marker)
  - utilizes or complements laboratory work

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Review Process: Plan Ahead

- Competing political agendas of senior staff?
  - touch base with appropriate staff to make sure they are on board
  - make sure you have thought of all potentially involved departments- Radiology, Surgery, Medicine
  - will your protocol affect the pattern of patient care?
  - know who needs to approve your protocol

    department chairs, program leaders, head of nursing, lab, or clinical trials office

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Review Process: Plan Ahead

- What committees will review your protocol?
  - Cancer Center Protocol Review Committee
  - Operations committees
  - Institution Review Board
  - Departmental or Program committees
  - Biosafety, Radiation Safety, and Radioactive Drug Research
- Make sure you are prepared for these committees, even if you are not present during their deliberations

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Investigator Role

- Leader of the study team
- Selects members and delegates tasks
- Directs study activities
- Evaluates performance
- Bears final responsibility
  - patient safety & welfare
  - quality control
  - integrity and scientific merit of findings

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Write the Protocol !!

Plagiarize & polish

- A previous protocol from your institution or a cooperative group can be a solid guide
- Be careful to clean up cutting and pasting from previous protocols
- Imagine the background section will be used for the introduction and discussion of a grant or eventual publication on the protocol
- Check with clinical trials office and local IRB for generic informed consent forms

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Template for Study

1. Title Page
2. Synopsis (1-2 pages)
3. Table of Contents
4. Introduction- background, rational, and toxicity
5. Objectives
6. Eligibility Criteria
7. Procedures for Patient Entry on Study
8. Methodology & Study Schedule
9. Adverse Events and Treatment Modifications
10. Data and Safety Monitoring
11. Statistics and Data Analysis

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Protocol Synopsis

- The study objectives
- A basic description of the study design
- The number of subjects to be enrolled
- Summary of inclusion and exclusion criteria
- The dosage regimen or device utilization plan
- Planned study procedures
- The planned methodology for statistical analysis
- (1 to 2 pages)

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Design: Objectives

- The primary objective is will drive your design, statistics, and accrual goals (e.g. survival)
- Secondary objectives may include related measures of results (e.g. response)
- Secondary and exploratory objectives may look at completely different issues (e.g. cost analysis, response predictors)
- Make sure the main objective is one that is clinically or scientifically meaningful
- Think about reporting for ClinicalTrials.gov, so keep secondary objectives simple

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Statistical vs. Clinical Significance

- A good study will yield both
- Statistical
  - probability that a finding is true
- Clinical
  - the contribution a finding makes to medical practice
- Carefully consider the number of patients required
  - Consented patients (screen failures)
  - Completed some intervention
  - Evaluable

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Pitfalls in Protocols: Eligibility

- Write eligibility carefully-- or it will come back to bite you
- Do not include unnecessary conditions, that you will be tempted to ignore, such as limits on:
  - acceptable labs (e.g Hgb >9, creatinine)
  - co-morbid conditions
  - prior malignancies
  - prior treatments
  - results from standard imaging techniques ("measurable disease")
  - NO waivers for eligibility
- Make sure you eliminate patients that are too sick or complex to really evaluate

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Pitfalls in Protocols Eligibility Examples

- 69y/o F Treated BURKITTS lymphoma in 2009
  - Thyroid microcarcinoma (1.5mm) treated in 2011
  - 2015 newly diagnosed unresectable head of pancreas adenocarcinoma with infiltration of vessels and adjacent organs
  - NOT eligible for advanced pancreatic protocol– WHY?
- All previous treatment related grade 2 adverse events must resolve to grade 1 prior to enrollment
  - NOT eligible due to persistent neuropathy
- Previous treatment of a glioblastoma with surgery & radiation
  - Disease and treatment related paraplegia
  - NOT eligible due to Performance Status 2

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Evolving Eligibility Criteria in SWOG Phase III Lung Cancer Trials (1995-2014)

Criteria	S9509 1996	S1400 2014
Brain Metastasis	NO	Yes (Treated)
Prior Malignancy	Skin, Cervical Others >5 yrs	Stage I-II CR OK Skin, Cervical Others >5 yrs
HIV status	No mention	Yes (controlled)

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Screening Procedures Prior to Study Entry

- Make sure the timing of procedures is appropriate
  - if screening is done too far in advance of enrollment; lab or imaging may have changed.
  - if evaluation must be done just prior to the start you may need to repeat lab and imaging.
  - generally, imaging can be done up to 4 weeks before treatment and labs within 7- 14 days.
  - insurance will often not cover imaging if too frequent.
  - screening that is not part of standard of care may need to be paid for by the study.
- Consent procedure:

  Make sure patient and investigator sign consent before starting protocol or pre enrollment screening procedures that are not part of standard of care.

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Study Calendar

TASK	Baseline visit	Day 2	Day 7	Day 14
Screen for eligibility	x			
Obtain informed consent before labs	x			
Vital signs	x	x	x	x
EKG	x			x
Patient history	x			
Hematology & Serum Chemistry	x		x	x
Urinalysis	x			
PHYSICAL EXAM: *Complete*	x			
Brief		x	x	x
ASSESSMENT: *Pain*	x	x	x	x
Inflammation	x	x	x	x
Adverse Event	x	x	x	x
Dispense Medications	X		x	
Retrieve unused meds & containers			x	x

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Study Structure: Testing and Timing

- Make sure every test listed during a protocol is really needed:
  - Non-standard of care tests are often missed and considered a deviation
  - e.g. monthly serum phosphorous levels
- Make sure timing of tests & treatments are reasonable
  - e.g. pre-treatment drug level to be drawn "+/- 5 min" after infusion, where -6 min is a deviation!
  - Better: Time between tracer injection and imaging should be less than 10 min between the baseline and the follow-up scan. If time is between 10-15 min a variation is recorded, but patient stays on study

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Data Collection

- Data collection and management of a clinical trial currently accounts for up to 60% of the overall clinical trial process
- Electronic case report forms streamlines the clinical trials process by capturing, processing and managing the clinical documentation

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Design: Budget

- Develop potential sponsors
  - Internal seed money
  - Grants
    - Funding Institutions, NIH
      - program announcements
      - unsolicited investigator initiated grants
      - SBIR grants
  - Industry
    - Pharmaceutical manufacturers
    - Medical device companies
    - Contract research organizations

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Design: Budget

- All protocols cost money, even if it is just your own time (e.g review of previous clinical experience)
  - regulatory and review costs
  - physicians and nurses recruiting patients
  - physicians and nurses to follow-up results of treatment or imaging
  - laboratory tests that are not part of the standard of care
  - data management costs
  - Imaging costs: machine time, tech support, supplies
- Some of these costs may be hidden and not explicitly charged, but they are all real

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Prestudy Documents

Protocol
Informed consent
HIPAA
Cancer Center Submission Form
IRB Submission Form
Radiation Safety Application
Investigator's and sub-investigator's CVs
Form FDA1572 completed for all investigators
Current laboratory ranges
Laboratory's accreditation certificate

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Protocol Review

- **Protocol Review Committee will assess:**
  - **scientific and clinical rationale**
  - **competing protocols and prioritization**
  - **ability to accrue patients**
  - **statistical review**
  - **treatment plan and safety (this group will have the better expertise than the IRB)**
  - **use of Cancer Center resources (funding)**
- **Radiology input in the PRC can be variable, so be prepared to have your protocol reviewed by clinical oncologists.**

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Institutional Review Board

- Safeguards the rights, safety and well-being of all trial subjects
- Reviews protocol, amendments, recruitment procedures, payment & compensation to the subject and PI's qualifications
- IRBs
  - Local IRB at your university or hospital
  - NCI Central IRB
  - Commercial IRBs (WCG, Advarra etc)

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Protocol Review

- Institutional Review Board or Human Investigation Committee Includes:
  - Physicians, scientists, statisticians, lay public
  - less likely to include radiologists
- Will assess:
  - Safety -- but may have limited expertise for your specific protocol
  - Consent form -- completeness, readability, explain medical terms, e.g. low platelets
- Hopefully, your IRB has developed standard wording for common issues such as risks of standard procedures, confidentiality issues, treatment of side effects or problems.
- More Radiologists should join PRC and IRBs

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Design: Adequate Accrual

- Plan for accrual management; prepare remedies for contingencies
- Consider communication of protocol to physicians and practice groups
  - all communication must be IRB approved
- Include talking points showing the merits of research
- Consider publicity for potential patients through brochures, posters, newsletters, the web (IRB approved).

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Design: Protocol Revisions

- Despite careful planning - they occur
  - certain aspects of the plan may be unworkable in practice
  - circumstances change (adverse event, shortage of subjects)
- Implement when a change will reduce risk to subjects
- NO waivers, but deviations may be allowed

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Integration: Good Clinical Practice Source Documentation

- First place a clinical observation is recorded
- Supports a study's findings
- Legally valid raw data
- Establishes an audit trail
- Tells the complete story of the subject
- Nothing should be assumed. If it is not documented it theoretically did not happen.

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Quality Assurance Committee

- Cancer Centers QAC will compare study records to make sure the protocol is followed

All deviations are reported for the investigator to address:

- Patients meet all eligibility criteria:
  - Laboratory values not in range
  - Tests (e.g. CT) that are too old
- Study procedures are followed:
  - All tests and procedures are completed, even if judged non-essential by the investigator
  - The exact timing of treatments and procedures is followed- make sure you allow for reasonable variation

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Points to Remember

- Source documents include medication charts, patient diaries, traces and printouts from automated machines and even appointment diaries
- Make sure there is sufficient evidence in a subjects chart to justify patient eligibility- use a check list
- Data must be recorded on study specific CRFs
- It must be possible to reconstruct CRFs using data recorded in the patient file

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Documentation for Adverse Events

- An adverse experience (also called event, AE) is any untoward medical occurrence in a trial subject who has been administered a pharmaceutical product
- AE may have no relationship to the treatment
- Prompt reporting to the sponsor and IRB
- If AE is severe or alarming the PI must report it immediately (within 24 hours);

  21 CFR Part 312.64 (b)
- In an imaging study one may limit AE to those that occur for a short time after the procedure

  (e.g. 2 hours)
- For therapeutic trials one will usually report AE for up to 30 days after treatment

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Safety Reporting

- Laboratory abnormalities may also be classified as AEs
- Good documentation is needed to summarize medical occurrences of SAE:
  - results in death
  - is life threatening
  - requires in-patient hospitalization
  - prolongs existing hospitalization
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

When in doubt report it-RAPIDLY !!!

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Imaging Response to Treatment

- The protocol may need to
  - define how imaging should be done
  - include technical details such as use of contrast or tracer, instrument specifications, training of readers, etc.
- Be careful to limit specifications to those that are essential or you may:
  - disqualify patients
  - limit the sites that can participate
  - interfere with the usual work flow in the Radiology Dept
  - limit the generalizability of the study to a few "experienced" academic sites
- Some therapeutic protocols give no direction on how the imaging should be done or even the type (e.g. "CT or MR measurement is needed").

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Imaging Response to Treatment: Problems

- RECIST criteria are difficult to use as part of routine care:
  - scans are often done away from academic medical centers due to distance and/or insurance
  - readers often don't measure lesions, especially the 5 required by RECIST
  - measuring irregular and ill defined lesions is arbitrary
  - the most recent scan is usually compared to the last scan, not the pre-treatment or best-response scan
  - different readers may read scans over time
  - new targeted therapies may not shrink lesions

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Imaging Response to Treatment: Problems

- We regularly see reports that:
  - describe the tumor as "slightly better or worse"
  - give measurements that are not consistent with the previous reading
  - make it hard to tell what lesion or where a lesion was measured
- Please:
  - give measurements
  - look at previous measurement
  - record the slice used to measure the lesions
- It is always simpler when there are new lesions, since that is automatic progression

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Conclusions

Careful planning of clinical trials is essential to their successful conduct.

Make sure that you have thoughtfully defined:

- eligibility
- pre-study procedures
- study calendar
- treatment
- dose adjustment
- data collection forms

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Conclusions

During the trial make sure that you have adequate:

- consenting
- use of an eligibility checklist
- treatment compliance
- data collection
- reporting adverse events
- documentation
- accurate outcome measurements

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