

Understanding Clinical Trials



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What I Hope to Teach You

- What a clinical trial is
- What different types of trials are available
- What the components of a good clinical trial should be
- How clinical trials work



What is a Clinical Trial?

- A clinical trial is a *research* study that uses human *volunteers* to answer a scientific question
- Scientifically and ethically approved
- Reviewed at regular intervals
- Requires *informed consent*



Why are Clinical Trials Conducted?

- To improve existing treatments
 - More effective in controlling disease
 - Less toxic to the patient
 - Late effects studies
 - Less time consuming, less expensive
- To understand disease better
 - Tissue studies
 - Tissue banking: future research
- To link our understanding of disease to treatment outcomes



The Research Question

- Clear and attainable
- Answerable in a definitive manner
- Statistically analyzable
 - Sample size
 - Significance and confidence
- Scientific review boards assess trials for these qualities



Research Ethics Boards

- Purpose: to ensure the safety of human volunteers
- Guided by internationally established principles
- Composed of scientists, doctors, ethicists, lay persons, clergy, lawyers
- Pay particular attention to consent forms
- Review studies annually for participation, safety issues



Different Kinds of Trials

- Drug development or treatment approaches go through stages, or phases, of study
 - I, II, III, (IV)
 - Pilot Studies
- Patients encounter studies in reverse order



Phase III Clinical Trials

- Compares standard therapy with an experimental therapy
 - Standard therapy: considered best known; results of these are usually published
 - Experimental therapy: considered to be at least as good
- Involve randomization(s)



Phase III Trials

- Have more liberal eligibility criteria
 - Proven diagnosis, adequate organ function
- Involve large numbers of patients
- Will usually be analyzed by “intent to treat” (vs treatment received) to reflect reality
- Have “stopping rules” to ensure that an inferior arm of therapy will not be used too long
- Will often result in a change in standard therapy



Phase II Clinical Trials

- Determine if a new drug or treatment approach is active against specific tumors
 - What types of tumors are these new drugs active against?
- Do not compare treatments
- Describe more of the toxicity of the drug
- Require a lower number of patients to answer the research question
 - May open and close to enrollment to allow periodic analyses
- Active drugs will be incorporated into Phase III trials



Eligibility for Phase II Trials

- Patients whose first-line therapy has failed
- Patients with high-risk diseases for which standard therapy is not very good
 - Phase 2 “Window”
- Number of prior therapies may or may not be restricted
- Patients must nearly always have disease that is measurable



Phase I Trials

- Seek to determine the maximum tolerated dose (MTD) of an agent
- Do NOT seek benefit
- Seek to determine the side-effects of an agent
- Highly regulated; limited institutions
- Despite these, offered with hope



Phase I Study Eligibility

- No known curative therapy or no acceptable standard therapy must exist
- Phase III and II treatments have failed (or aren't available [Phase II])
- Criteria include measures of "performance" or "play" as measures of overall wellness



Phase I Study Accrual

- Patients studied usually in groups of three at a time
 - Studies open and close as these groups are monitored for side-effects
- Must receive and recover from a certain dose before others may be treated
- The MTD is the dose below which patients have unacceptable side-effects
- The MTD will be used in Phase II study



Pilot Studies

- May be Phase I, II or combined
- Test do-ability



New Drug Development

- Pre-clinical testing
- Animal testing
- Adult, then Pediatric Phase I trials
 - These seek MTD
- MTD used in Phase II:
 - Activity against specific tumors is identified
- Active Phase II agents are incorporated into Phase III studies
 - Compare new vs standard treatments
- The entire process may take 10 to 12 years



Patients' Encounters with Clinical Trials

- Start with Phase III or II
- Only when front-line therapy fails is Phase II offered
- When no other curative therapies are known, Phase I may be offered



Components of Clinical Trials

- Goal is to conduct sound research
- Human subjects must be uniformly diagnosed and treated
- Hypothesis: a proposed explanation of an observation or effect sought
- Objectives: the specific research questions or goals of the study
- Background and Rationale
- Drug Information



Components of Clinical Trials: ii

- Patient eligibility and exclusions
- Treatment Plan
 - Surgery, chemotherapy, radiation therapy
 - Dose modifications
 - Monitoring to take place
- Statistical analyses to be conducted
 - Definitions of response (or lack of)
 - How much improvement is being sought
 - To what degree of confidence the questions will be answered



Informed Consent: Components

- Who is conducting the study?
 - Research group; singles or limited institution(s)
- Objectives
 - Why is this study being conducted?
- Eligibility
 - Why are you (or your child) being offered this study?



Informed Consent: Components ii

- Treatment Plan
 - What will you receive, when, how, over what period of time
- What are the costs to you?
 - Insurance vs out-of-pocket expenses
- What are the potential risks and benefits to you?
- What are your options? What are the alternatives?



Special Considerations

- Phase III:
 - How does the experimental therapy differ from standard?
 - In benefit, risk, comfort to the patient
 - If you decline randomization, how will you be treated?
- Phase II:
 - Why this particular agent?
 - Will participation in other trials be jeopardized?
 - Can the drug be obtained without being on the study?
- Phase I:
 - Not much is known about the drug
 - Benefit cannot be predicted



Clinical Trials

- Copies of the trials are available to you upon request
- “Protocol”
 - The entire study
 - The treatment plan
 - Abbreviated treatment plan
- Vs institutional practice



Monitoring Clinical Trials

- By the research group (e.g. RTOG, COG)
 - For accrual and succession planning
 - For safety
- By Data Safety Monitoring Boards
 - No investment in the studies
- By Institutional Review Boards
 - Must assure that patients in their institution are protected



Biological Trials

- Generally involve the collection of tissue from patients:
 - Tumor, blood, urine; skin, DNA
 - Non-tumor tissue provides comparison of a person's tumor to her or his healthy self
- Participation may have immediate impact on therapy
 - e.g. Results of cytogenetic testing may direct randomizations
- Will generally ask permission to “bank” samples
 - Additional questions re banked samples
 - Research on cancer, non-cancer diseases
 - Results and being informed



Inherent Tensions in Clinical Trials

- Your doctor as a researcher vs a physician
- The clinical trial for everyone vs individualized therapy for you
- Randomization: Does your doctor have a bias, either spoken or unspoken?
- So much to learn in so short a time under the worst of circumstances
 - Can consent ever be “informed”?
- What if you say “no”
 - Standard therapy; no impact on relationship
- Unfavorable outcome and long term psychoemotional burden



Results of Clinical Trials

- Cure rates for many tumors have risen
 - However, comparatively little progress in high-risk tumors
- Toxicities, both acute and long term, have been decreased
- On the whole, treatment on clinical trials yields superior outcomes



Clinical Trials and You

- Access to best known treatment is possible without enrollment on a clinical trial
- Favorable outcomes cannot be guaranteed whether on a study or not
- Enrollment is voluntary and requires consent
- You should enroll only after you understand the study as well as you can and have had all of your questions answered