NMST532 Design and Analysis of Medical Studies

Slide set I.

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Clinical trials in drug development

- We will describe the process of development of a new drug
- Approval of new drugs is regulated and requirements are strict
- An important role in the process play randomized clinical trials
- Many steps require carefully planned and presented statistical analyses

Stages of drug development

Pre-clinical

1. In vitro research: evidence of biological effect
2. Animal studies: pharmacokinetics, toxicity, efficacy, dose specification, carcinogenicity, teratogenicity

Clinical

1. Phase I. Pharmacokinetics, toxicity
2. Phase II. Safety, efficacy, dose finding
3. Phase III. Effectiveness, safety $\Longrightarrow$ **APPROVAL**
4. Phase IV. Post-marketing studies

Pre-clinical stages

1. In vitro research
   - Looking for chemical compounds with desired biological effect
   - Basic lab research
   - Sometimes starts with modifications of current drugs
2. Animal studies
   - Verification of suggested in-vitro effects
   - Pharmacokinetics: concentration of drug in blood over time
   - Means and modes of drug metabolization
   - Toxicity: potential to harm living organisms
   - Look for safe dose ranges
   - Reveal harmful side effects (carcinogenicity, teratogenicity)

Animal studies

1. Necessary to gather important information
2. Cannot be dispensed of (no computer models are good enough)
3. Subject to ethical approval
   Principles: minimize harm, no unnecessary suffering, no painful procedures

Pre-clinical stages

Statistical involvement in pre-clinical stages

1. Pharmacokinetic analyses
2. Toxicity analyses (LD50 = lethal dose 50)
3. Standardized methods, can be done automatically

Human experiments

1. Human experiments consist in several successive phases of clinical trials
2. Preceding pre-clinical research (labs, animals) must demonstrate a promise in desired effects of the drug and its tolerability
3. Most candidate drugs are too toxic to proceed to human experiments

Human experiments

4. If the drug is to be eventually approved for marketing *it is mandatory to register all human trials with a regulatory agency*[1] and to follow strict guidelines about the conduct of the trials
5. Ethical approval from accredited Institutional Review Boards (IRB) is required
6. Results of intermediate trials and decisions about further steps must be reported to the regulatory agency

[1] In the U.S., the agency is called Food and Drug Administration (FDA)

Phases of human clinical trials

Clinical trials are done in 3–4 phases. Each phase is started only if the previous phase was successful.

1. Phase I. Initial human trials focused on dose escalation, pharmacokinetics, immediate toxicity
2. Phase II. Intermediate trials focused on safety, preliminary efficacy, dose selection
3. Phase III. Ultimate trials focused on effectiveness and safety, lead to drug approval
4. Phase IV. Post-marketing trials focused on additional information on effectiveness, long-term safety, cost-benefit ratio

Phase I clinical trials

- Small studies (a few individuals up to several dozen), short duration
- Population: healthy volunteers, terminally ill patients
- No randomization, frequently no control arm
- Sequential designs, dose escalation
  - start with a single low dose
  - increase the dose up to some safe level
  - proceed to repeated dosing starting from a low dose
- Endpoints: pharmacokinetics, adverse events, monitoring of body functions
- Statistics: mainly descriptive

A drug that shows satisfactory results in a Phase I trial proceeds to Phase II.

Phase II clinical trials

- Moderate size studies (several dozen to a hundred), follow-up duration a few weeks
- Population: selected patients with the disease to treat
- Usually randomized, with placebo arm (but not always)
- May compare several doses of the drug selected by Phase I results
- Endpoints: markers of immediate efficacy, safety (adverse effects)
- Statistics: focused on significant improvement of efficacy endpoints

A drug that shows satisfactory results in a Phase II trial proceeds to Phase III.

Phase III clinical trials

- Large studies (several hundred patients), follow-up duration a few weeks up to several years
- Population: selected patients with the disease to treat
- Must be randomized, with placebo/control/standard therapy arm
- Includes one or two doses of the drug selected by Phase II results
- Endpoints: markers of effectiveness, safety (adverse effects)
- Statistics: must show a significant improvement of effectiveness endpoints

A drug that shows a significant effect in a Phase III trial can be approved for production/marketing/clinical use.

Phase IV clinical trials

- Further investigation of drugs that have been already approved
- Studies of various sizes and durations
- May or may not be randomized, with placebo/control/standard therapy arm
- Potential purposes:
  - Investigate long-term safety or effectiveness
  - Investigate effects in marginal patient populations (children, pregnant women,...) that were not included in Phase III study
  - Investigate combinations of approved treatment regimens, drug interactions
  - Evaluate and compare cost-effectiveness of various treatment options

Role of pharmaceutical companies in drug development

- Pre-clinical development is done prevailingly by research institutions
- Human experiments starting with Phase I need to be run by pharmaceutical companies
- Clinical studies are extremely expensive, the investment is huge
- The full price of development of a new drug can be in the order of billions of USD
- The large majority of investigational drugs does not ever make it to approval or production (much less than half of the trials at each phase are successful)
- New drugs are made under an exclusive patent and are expensive in order to cover the development costs

Role of regulatory agencies in drug development

- All steps of the clinical stage of drug development are heavily regulated
- All trials starting from Phase I must be registered and undergo a review by the agency
- All study procedures must be written down in advance in the Study Protocol and in operating manuals and approved by the agency
- Data and program code for their processing and analysis are submitted when the trial is closed; all data manipulations must be revealed and justified
- Results are reported and reviewed before the permission to continue the development is given
- No other human activity is regulated and controlled so strictly