

1. Overview of Clinical Trials

§1.1. What are clinical trials?

Definition

A clinical trial is a planned experiment which involves patients and is designed to elucidate the most appropriate treatment of future patients with given medical conditions.

E.g., trials for new developed vaccine on H1N1; trials for different treatments on cancer patients, trials for new drugs, etc..

Historical examples

- A comparative trial of the most promising treatment for scurvy in 1753: 12 patients involved; Six daily treatments compared: **a** quart of cider, **25** gutts of elixir vitriol, **two** spoonfuls of vinegar, **a** course of sea water, **two** oranges and one lemon, **the** bigness of a nut-

meg; each treatment assigned to two patients; it concluded that use of oranges and lemons had significant good effects.

- Trials of bleeding as treatment for pneumonia, erysipelas and throat inflammation in 1835: Bleeding had been a standard treatment for these and other diseases. The trials found no significant effect of bleeding and instigated eventual decline in bleeding as a treatment.
- Trials of treatment of war wounds by using penicillin: severely wounded were given penicillin and compared with others without being given penicillin. A biased trial but still produce significant results.

Drug trials of pharmaceutical industry:

- *Phase I trials:* Clinical pharmacology and toxicity. The purpose of phase I trials is to determine drug safety rather than efficacy. It

involves determination of doses, multiple dose schedules, etc.

- *Phase II trials*: Initial clinical investment for treatment effect. A phase II trial is a small scale investigation into the effectiveness and safety of a drug. It can also be set up as a screening process to select out relatively few drugs of potential from a larger number of drugs which are inactive or over-toxic.
- *Phase III trials*: Full-scale evaluation of treatment. A phase III trial is a full scale investigation. The new drug must be compared with current standard treatment to determine its relative efficiency.
- *Phase IV trials*: Post-marketing surveillance. It is for monitoring adverse effects and long-term studies of morbidity and mortality.

§1.2 General procedure and principles of clinical trials.

A clinical trial is a complex undertaking that needs careful design and good organization.

General procedure

- Step 1: Define the purpose of the trial.
 - state specific hypotheses including the definition of (a) eligible patients, (b) treatment, (c) end-point measurements and (d) control group.
- Step 2: Design the trial.
 - a written protocol including 1) Background and general aims, 2) Specific objectives, 3) Patient selection criteria, 4) Treatment schedules, 5) Methods of patient evaluation, 6) Trial design, 7) Registration and randomization of patients, 8) Patient consent, 9) Required size

of study, 10) Monitoring of trial progress, 11) Forms and data handling, 12) Protocol deviations, 13) Plans for statistical analysis, 14) Administrative responsibilities.

- Step 3: Conduct the trial.
— needs good organization.
- Step 4: Analyze the data.
— descriptive statistics, tests of hypotheses, statistical methodology, etc.
- Step 5: Draw conclusions.
— reports and publication.

An example

Evaluate whether the drug L-Pam was of value in the treatment of primary breast cancer following a radical mastectomy.

- **Purpose of the trial:**

L-Pam caused temporary shrinkage of tumors in advanced breast cancer patients. It could be effective in killing off undetected tumor cells present after mastectomy in primary breast cancer patients.

Eligible patients: a radical mastectomy for primary mastectomy; histologically confirmed axillary node involvement; without complications such as peau d'orange and skin ulceration, etc.; age less than 75; not pregnant or lactating.

Treatment: L-Pam at 0.15 mg/kg for 5 consecutive days every 6 weeks; reduce dose by half while platelet $< 100,000$ or white cell $< 4,000$; discontinue drug while platelet $< 75,000$ or white cell $< 2,500$; dose increase to 0.2 mg/kg after three courses for patients with-

out toxicity; stop until treatment failure or for two years.

End-points: disease free interval; survival time.

Control group: standard treatment — radical mastectomy without subsequent L-Pam.

● **Design of the trial**

A few salient points emphasized below.

— number of patients required is of the order of several hundred, a multi-center trial with 37 hospitals participated.

— patients were stratified by age, nodal status and institution, patient was randomly assigned to receive either L-Pam or a placebo within each stratum.

— trial was double-blind.

— patients were to have follow-up examina-

tion every 6 weeks.

- **Conduct of the trial**

- trial committee meet periodically to assess progress and make alterations.

- informed patients consent obtained.

- protocol violations recorded.

- patients withdrawals with reasons recorded.

- a central coordinating office for monitoring patient entry, supervising data collection, etc.

- **Data analysis**

- survival curves were estimated and compared.

- age as a prognostic factor is analyzed on its influence on the effect of L-Pam.

- in addition to the final analysis, an interim

analysis was carried out.

- **Conclusions**

- L-Pam is effective.
- It is more efficient on younger women before menopause than on older women.
- For publication, the purpose, design and conduct, analysis and conclusions must be clearly described and discussed, concentrate on objective statements of factual evidence, make less subjective opinions.

General principles

- **Comparativeness**
 - there must be well defined comparison groups.

- Unbiasedness
 - randomization, control for prognostic factors, double blinding, placebo, etc..
- Assurance of ethic
 - patient consent, harmlessness, ethical consideration in process of trials.

§1.3 Statistical designs at a glance

Statistical designs are needed for clinical trials to have a scientific ground. The purpose of statistical designs is to guarantee unbiasedness and improvement of efficiency. It is achieved through different schemes for random assignment of patients and for controlling of prognostic factors.

Characteristic situations of different designs

- **Parallel groups design:** patients can be considered as homogeneous by the nature of the treatments, no prognostic factors to be controlled, only random assignment is needed.
- **Randomized block design:** patients can be matched by a block factor, the number of treatments to be compared is the same as the number of patients matched in each block, patients within each block are randomly assigned to treatments.
- **Stratification:** patients cannot be matched neatly as in randomized block design, there are different number of patients at different levels of the blocking factor, at each level of the blocking factor a parallel groups design is required.

- **Latin square and Greco-Latin square design:** blocks are formed by different levels of two or more factors, different treatments cannot be applied simultaneously within a block.
- **Cross-over design:** individual subjects might cause different effects of the same treatment, it is designed to control the individual subject effect.
- **Balanced incomplete block design:** situation similar to random block design but block size cannot be made the same as the number of treatments.