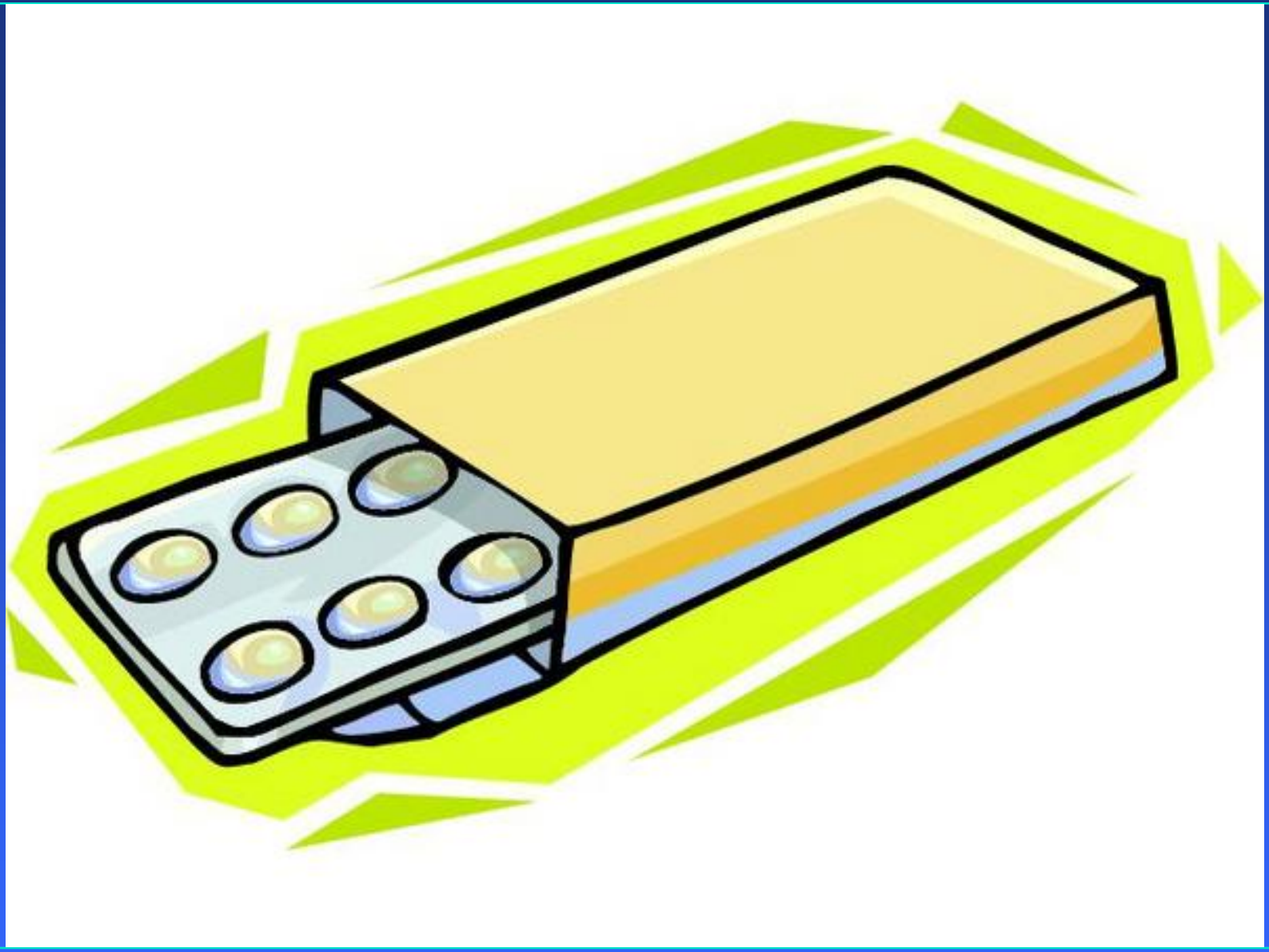
Planning a Clinical Trial

Clinical Trials

- Testing a new drug
- Ethical Issues
- Liability and Indemnity
- Trial Design
- Trial Protocol
- Statistical analysis



Clinical Trials

Clinical Development of a Drug

- **Phase I:** Tolerability (healthy volunteers)
- **Phase II:** Efficacy in target population
- **Phase III:** Efficacy and Comparison with current medication

Approval by regulatory bodies

- **Phase IV:** Confirmatory and post-marketing surveillance

Human Pharmacology (Phase 1)

- First human doses – usually healthy volunteers
- Estimation of initial safety and tolerability
  - Dose range
  - Single and multiple doses
- Pharmacokinetics (PK)
- Pharmacodynamics (PD)

Therapeutic Exploratory (Phase 2)

- "Proof of concept" (POC)
- Early testing of efficacy
- Narrow inclusion and exclusion criteria
- Small number of patients
- Dose and dose regimen for phase 3
- Multiple endpoints

Therapeutic Confirmatory (Phase 3)

- To demonstrate therapeutic benefit
- To demonstrate safety in a large cohort
- Extended exposure
- To provide adequate basis for marketing approval
- Typically RCT design
  - Multicentre
  - Multinational

Therapeutic Use (Phase 4)

- Begins after drug approval
- Within the approved indications
- For optimising drug use
- SAMM (post-marketing surveillance) Safety Assessment of a Marketed Drug
- A type of observational study with specific rules

Clinical Trials

Ethical Issues

The Declaration of Helsinky

- **Nuremberg Code** **1947**
- **WMA: Declaration of Helsinky** **1964**
- **Tokyo** **1975**
- **Venice** **1983**
- **Hong Kong** **1989**
- **South Africa** **1996**
- **Edinburgh** **2000**

Declaration of Helsinky

- Protection of patients rights
- Informed consent
- Independent approval
- Scientific/medical basis
- Appropriate risk: benefit ratio
- Subject well being takes precedence over other considerations

Clinical Trials

ICH- Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected

EU 2003
Medicine for Human Use Clinical Trial Regulations

- All clinical trials (Except non-interventional trials)
- Involving human subjects
- Involving medicinal products
- Commercial and non-commercial
- Within and outside the NHS

Principles of IH-GCP I

- Anticipated benefits to the subject, science and society justify the risks/inconveniences
- Scientifically sound, clear and detailed protocol
- Adequate pre-clinical and clinical data (pre-trial regulatory approval)
- Pre-trial Ethics Committee approval

Principles of ICH-GCP II

- Freely given consent prior to trial
- Medical care given by qualified doctor/dentist
- Suitably trained staff
- Trial supplies manufactured, handled and stored according to GMP
- Data management systems accurate
- Confidentiality of records
- Quality assurance of every aspect of the trial

Guidance Documents

The EU directives is supported by guidance documents:

- **Principles of GCP**
- **Authorisation for a clinical trial**
- **Ethics committee application**
- **Trial master file and archiving**
- **Qualification of investigator**
- **Qualification of inspectors**

- All trials require:
- A Sponsor who is responsible for :
  - The initiation of the study
  - The management of the study
  - Financing of the study
  - Monitoring that the trial is GCP
- An Investigator who is an authorised health professional, responsible for:
- Conduct of the trial
- The trial study team

Clinical Trials

Liability and Indemnity

Association of the British Pharmaceutical Industry (ABPI) guidelines (1988-1990):

- **The sponsor to compensate for injuries**
- **Compensation to be quick and fair**
- **Provision for arbitration**

Clinical Trials

Trial Design

- Ecological studies
- Case- Control studies
  - Retrospective analysis
- Cohort studies
- Randomised Prospective controlled trial (RCT)
  - Active control
  - Placebo control
  - Parallel/Cross-over

Global Kidney Academy

SHEFFIELD KIDNEY INSTITUTE

Sample size estimation

- 1. **Expected difference between groups (~20%)**
- **2. Power (probability of NOT getting a false negative result) (80%)**
- **3. Level of statistical difference (p value = probability that we have a False Positive) (<5%)**

Clinical Trials

Trial Protocol

- Background
- Aim
- Inclusion and Exclusion criteria
- Primary/secondary end-points
- Parameters
- Documentation (CRF)
- Monitoring
- Statistical analysis
- Reporting

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