Planning a Clinical Trial

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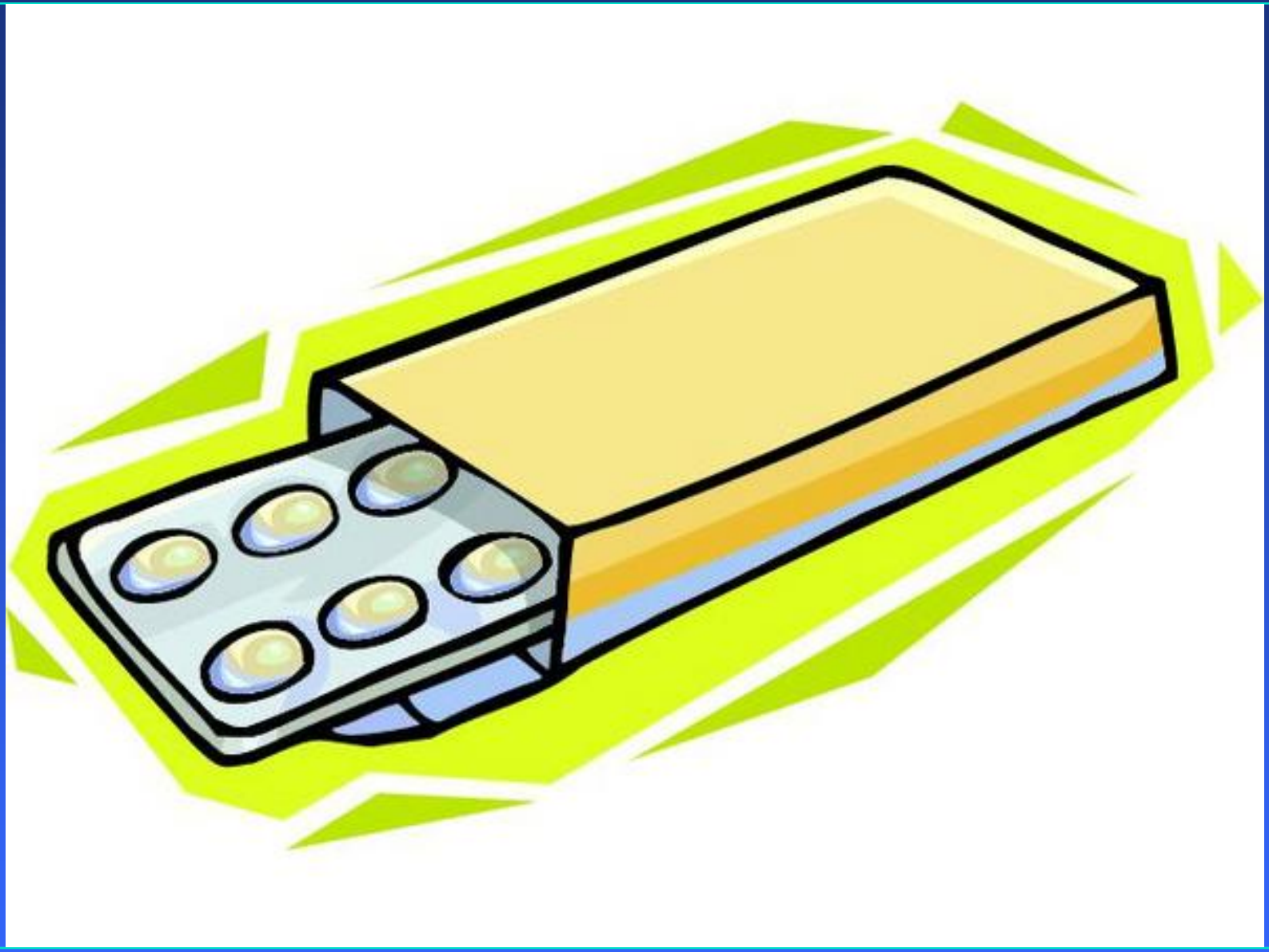
Clinical Trials

- 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

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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

Critical Appraisal of Clinical Trials

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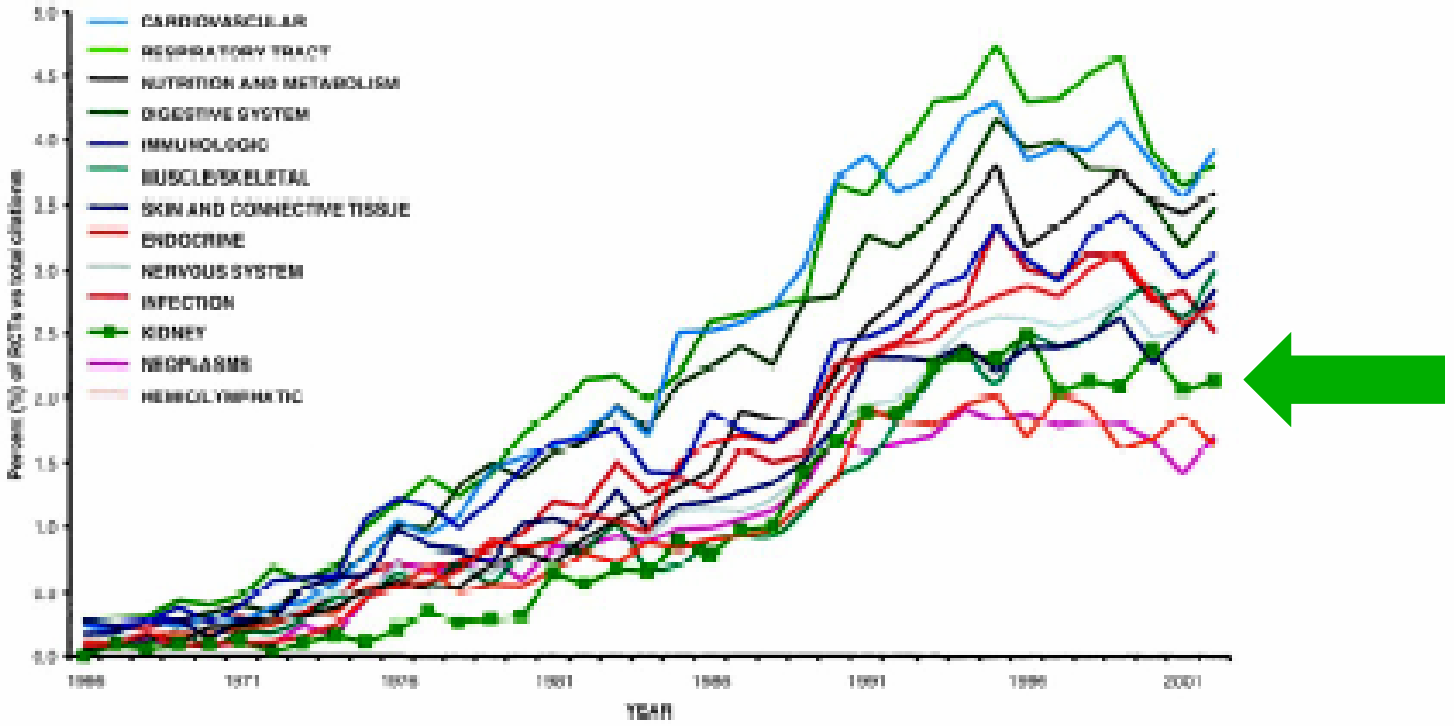

2. Percentage of RCT *versus* total citations in nephrology and 12 other specialties of internal medicine from 1966 to 2002.

"The Conviction with which many Nephrologists hold an opinion varies inversely with the Evidence…"

Ed Lewis

“The Good Old Times….”

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“The Google Generation….”

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ASN Kidney Daily

- **LEADING THE NEWS:**

+ Genetic Variant In Kidney Donors Linked To Increased Likelihood Of Graft Failure…

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Clinical Trials in Nephrology

- REIN
- DCCT
- Lewis Trial
- HEMO
- TREAT

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Stages in Appraisal Process

1. Skim reading

2. The Abstract/Message

3. What are the Results

4. Validity of the study?
5. Utility of the study?

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Hierarchy of evidence		
Level of evidence	**Description**	**No. studies**
1a	Systematic review of randomised, controlled clinical trials (RCT)	0
1b	Individual randomised controlled clinical trial	0
1c	All or none	0
2a	Systematic review of cohort studies	0
2b	Individual cohort study (including low-quality RCT)	0
2c	Outcomes research	0
3a	Systematic review of case-control studies	0
3b	Individual case-control study	0
4	Case series, poor quality cohort and case-control studies and reviews	14
5	Expert opinion without explicit critical appraisal	1
Other	Letter to the editor (5), Abstract (2)	7

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Critical appraisal of the medical literature

- **Validity:** Is the trial valid?
- **Utility:** Will the results help locally?

Is the study valid ?
Design

- **Was assignment of patients to treatment random?**
  - **Need robust randomisation, no chance that treatment allocation could be guessed. Details of randomisation should be given in methodology**
- **Is the study large enough?**
  - **Power of study (type II error – odds of accepting null hypothesis when actually the alternative hypothesis is true)**
  - **Is the number too small to generate a Type I error; false positive result?**
- **Were all patients who entered properly accounted for?**
  - **Patients who are lost to follow up not necessarily representative of whole cohort and may therefore bias results**
  - **Ensure follow up complete and similar in both treatment limbs**
  - **ITT rather than PP analysis**

Is the study valid ?
Analysis

- **Intention to treat analysis**
  - **Analysing groups to which they were randomised to rather than whether received treatment**
  - **If participants move between groups this distorts random generation of groups and may distort result**
- **Were the statistical methods appropriate?**
- **Was methods for dealing with missing information appropriate?**
- **Do results deal with whole data set or a specific subgroup?**

Appraising a Randomised Controlled Trial

Did the study ask a clearly focussed question?

Was this a randomised controlled trial?

Was it appropriately so?

Were participants appropriately allocated to intervention and control groups?

- The flip of a coin is a perfectly reasonable method of randomisation.
- Random Number Tables are good.

Are the groups well balanced?

Is there a Bias ?

Selection Bias

- Occurs when the method of drawing the sample affects the results of the study
  - Was the sample typical?
  - Could the method of drawing the sample favour or ignore certain participants?

Observer Bias

- **Occurs when those involved with the study* allow their knowledge of the study to affect the way observations are scored or recorded.**

Attrition Bias

- **Occurs when there are important differences between the number of participants lost to follow-up in the comparison groups**
- **Intention to Treat analysis says that data on *all* participants should be analysed with respect to the groups to which they were initially randomised.**

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Follow-Up and Drop-Out

- Patients who are lost often have different prognoses from those who are retained
- Researchers should check this by doing a calculation that assumes:
  1. Patients lost from the treatment group did badly
  2. Patients lost from the control group did well
- If the conclusions would change, then the strength of those conclusions is weakened

Data Analysis

- **ITT = Intention to Treat = ALL included in analysis**
- **PP = Per Protocol = ONLY those who finish the study included in analysis**

Performance Bias

- **Occurs when what was measured happened because of the study itself rather than the intervention.**
  - **Ask whether participants have been treated the same way throughout the trial (apart from the intervention)**

Is the Sample size adequate?

Getting a false negative

“Saying that there is NO difference between the control and intervention in the population, and being WRONG”

(Sometimes known as a Type II Error)

Getting a false positive

“Saying that there IS a difference between the control and intervention in the population, and being WRONG”

(Sometimes known as a Type I Error)

In search of a higher Power

- **The Power is expressed as a probability (between 0 and 1):**
- **The probability that you *won't* get a false negative.**
- **The higher the power, the more chance there is that *if there is* a significant difference, you *will* detect it.**

More about the Power

- **By convention, power is usually set at 0.8 (80%), by balancing effect size, sample size and uncertainty.**

- **If:**
  - **the number of participants recruited is lower than planned,**
  - **or the effect size is different than expected,**

  then the power will be lower, and the chance of getting a false negative will be *more than* 20%.

Sample size estimation

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Critical Appraisal

Process of assessing

- **Validity**
- **Usefulness of evidence**

Utility – will the results help locally?

- **Can results be applied to local population?**
  - **Are there differences between study and local population, must consider those participants not completing study**
- **Were all clinically important outcomes considered?**
  - **Consider whether other important outcomes have been highlighted or omitted**
- **Are the benefits worth the harm and costs?**
  - **Risk-Benefit analysis**
  - **Cost effectiveness**

Jadad Score

- Randomisation and allocation concealment
- Blinding
- Sample size/Power
- Analysis; ITT versus PP
- Drop out and Lost to follow-up

Validity

- **RCT :** **YES/NO**
- **Blinded:** **YES/NO**
- **Randomisation detailed:** **YES/NO**
- **Randomisation Bias** **YES/NO**
- **Sample size estimation:** **YES/NO**
- **Drop out >25%:** **YES/NO**
- **ITT analysis:** **YES/NO**

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Utility

- Applicable to my patient YES/NO
- Applicable to my country YES/NO
- Applicable to my socio-demographic environment
- Applicable to my health economics YES/NO

Critical Appraisal

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