Designing a Clinical Trial in Oncology

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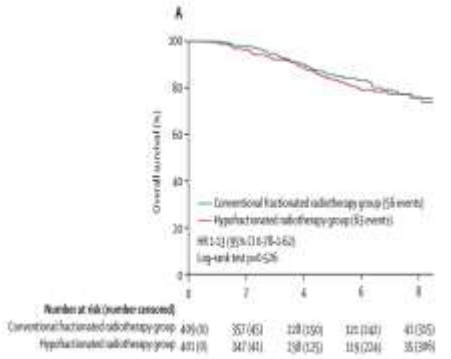
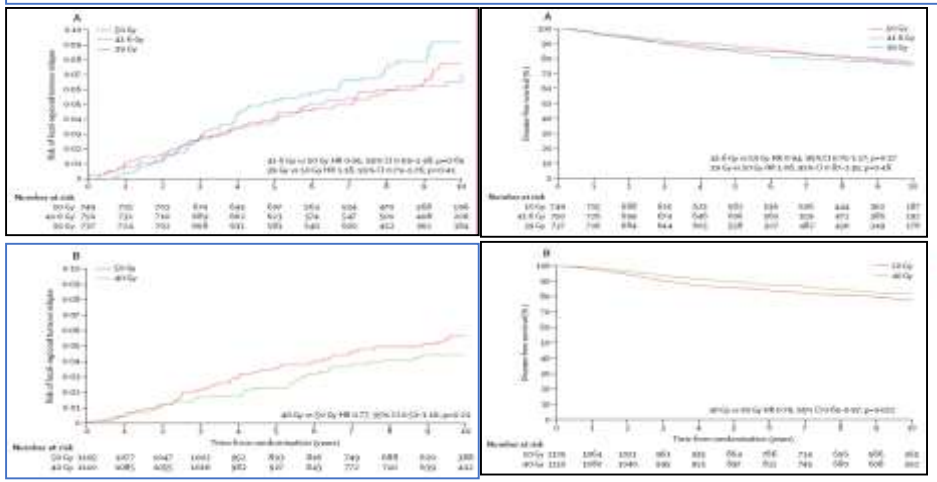
AIIMS

The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials

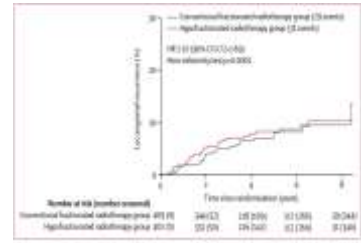
Joanne S Haviland, J Roger Owen, John A Dewar, Rajiv K Agrawal, Jane Barrett, Peter J Barrett-Lee, H Jane Dobbs, Penelope Hopwood, Pat A Lawton, Brian J Magee, Judith Mills, Sandra Simmons, Mark A Sydenham, Karen Venables, Judith M Bliss*, John R Yarnold*, on behalf of the START Trialists' Group†





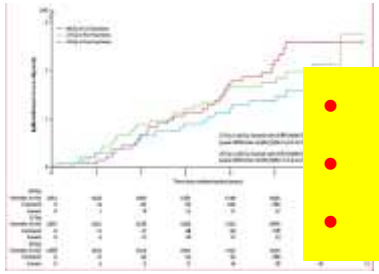
Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial

Shu-Lian Wang*, Hui Fang*, Yang-Wen Song, Wei-Hu Wang, Chen Hu, Yue-Ping Liu, Jing Jin, Xin-Fan Liu, Zi-Hao Yu, Hua Ren, Ning Li, Ning-Ning Lu, Yu Tang, Yuan Tang, Shu-Nan Qi, Guang-Yi Sun, Ran Peng, Shuai Li, Bo Chen, Yong Yang, Ye-Xiong Li



Not different between CFRT and HFRT

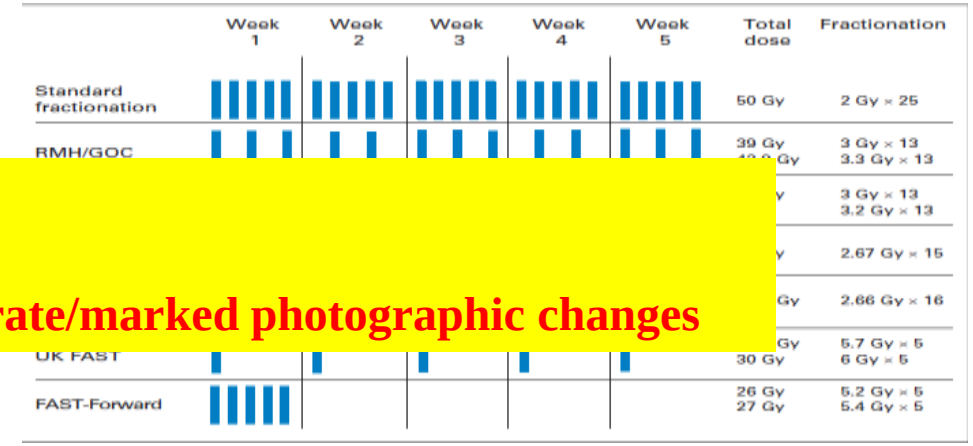
Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer



Systematic review and meta-analysis comparing hypofractionated

...breast radiotherapy for 1 week versus ...ks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial

Adrian Murray Brunt*, Joanne S Haviland*, Duncan A Wheatley, Mark A Sydenham, Abdulla Alhasso, David J Bloomfield, Charlie Chan, Mark Churn, Susan Clingor, Charlotte E Coles, Andrew Goodman, Adrian Harnett, Penelope Hopwood, Anna M Kirby, Cliona C Kirwan, Carolyn Morris, Zahal Nabi, Elinor Sawyer, Navita Somaiah, Liba Stones, Isabel Syndikus, Judith M Bliss†, John R Yarnold†, on behalf of the FAST-Forward Trial Management Group



- **HFRT cost one-third lower than CFRT**
- **Decreased grade 2/3 acute skin reactions**
- **HFRT 2.5-3.0 Gy /# significantly decreased moderate/marked photographic changes**

Why research/Clinical trial

Before Writing Phase: Feasibility, Study Aims, and Methodology

FINER

Feasible

Interesting

Novel

Ethical

Relevant

Why research/Clinical trial

- **Before Writing Phase: Feasibility, Study Aims, and Methodology**

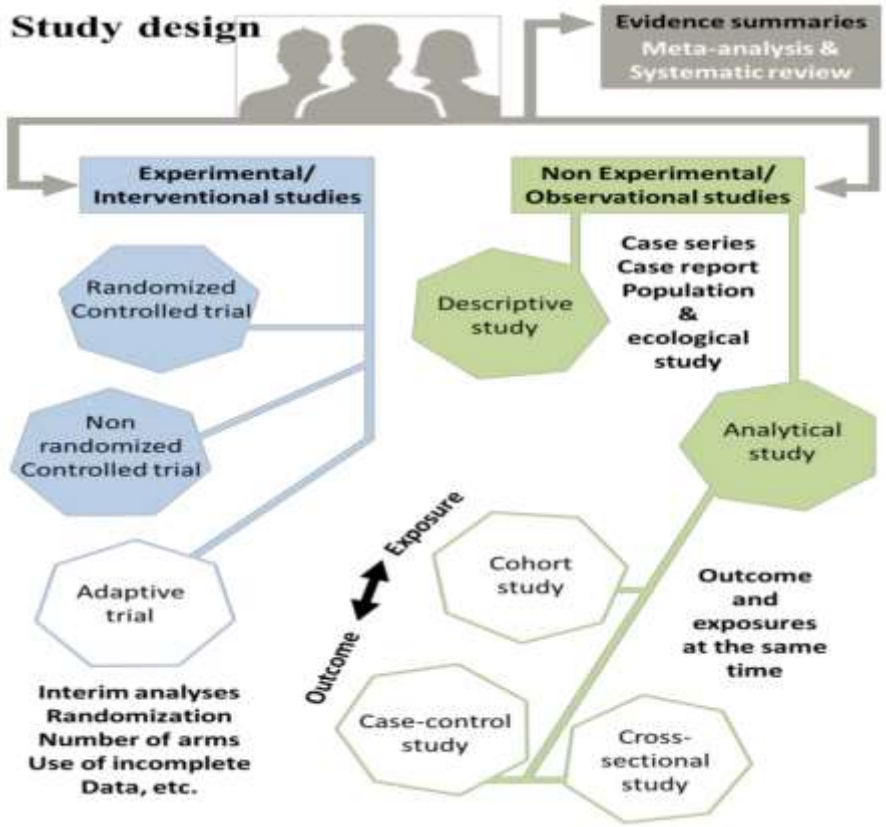
1. “What are the aims of the study?”

2. “Why, Where and How the study should be conducted?”

Hypothesis/research question

- Most Important
- **SMART**
  - Specific
  - Measurable
  - Achievable
  - Relevant
  - Time-frame

What type of trial/Design of trial



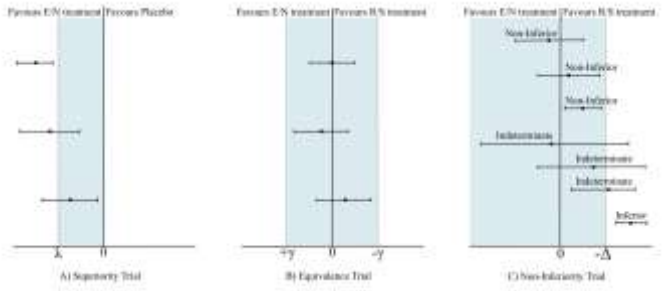
Randomized trial: Game of number

Trial Design	Interpretation
Superiority	Intervention > Control
Equivalence	Intervention = Control Eg a new drug is not "unacceptably different" compared to the standard
Non-inferiority	Intervention is not "unacceptably worse" than control The new drug may be meaningfully less efficacious compared to the standard but that lost efficacy is acceptable to us!

Particular intervention may be acceptably worse

But has ancillary benefits over the control such as lower costs, lesser side effects, easier administration etc.

Smaller sample size

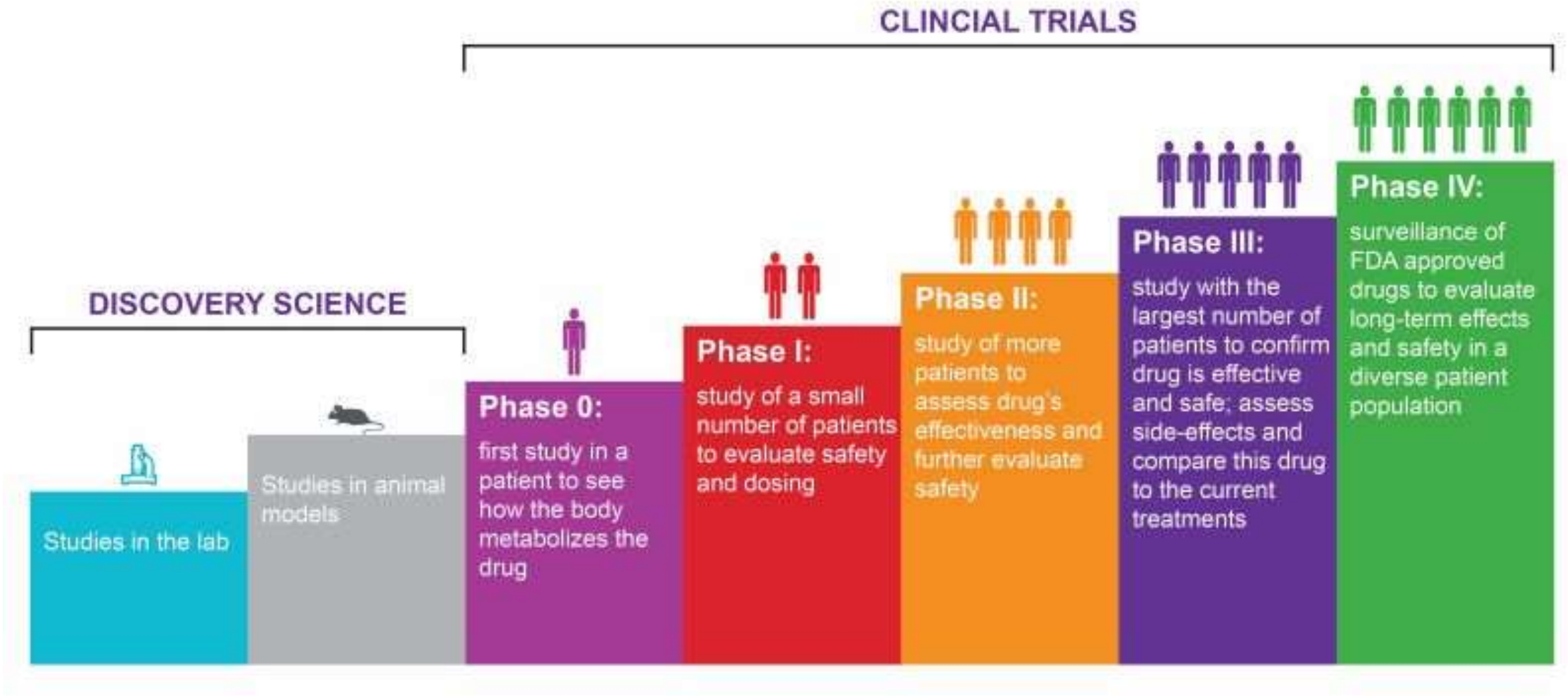


Adaptive trial design

Objective/ Define endpoint

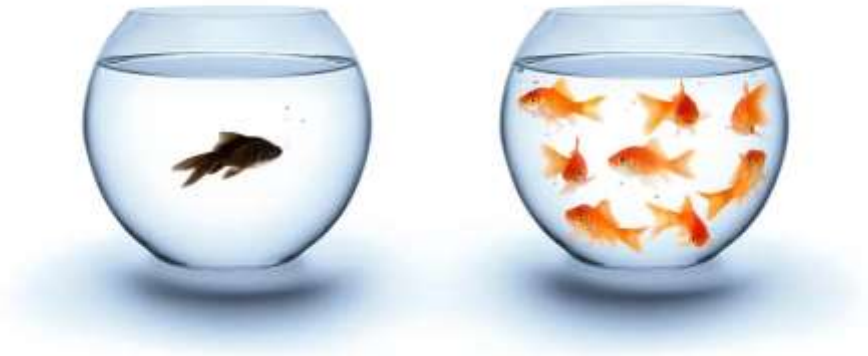
- Endpoints are the gateway to answering a research question
- Number of endpoints
- Primary and secondary
- Single trial; Single Intervention

Objective/ Define endpoint



Inclusion/Exclusion

- Study participants have the characteristics that will make it possible for the researchers to accomplish the study's purpose
- Increase the likelihood of the study producing accurate, reliable, and reproducible results
- Help ensure the safety of participants



- **Inclusion criteria: P**rospective participants must have
- **Exclusion criteria:** Disqualify prospective participants

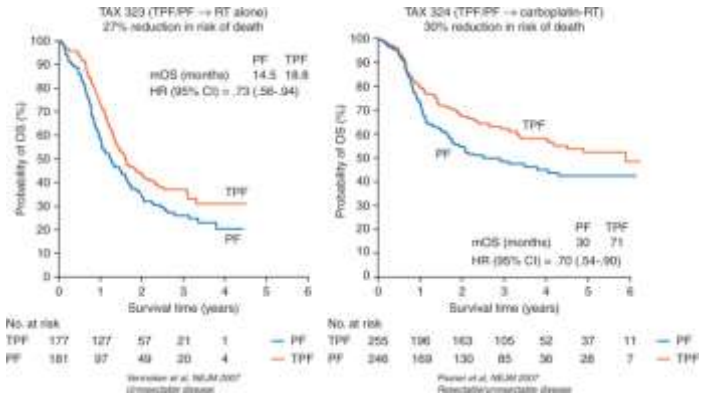
- Written using positive language, avoiding negative clauses

Intervention and Comparator

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

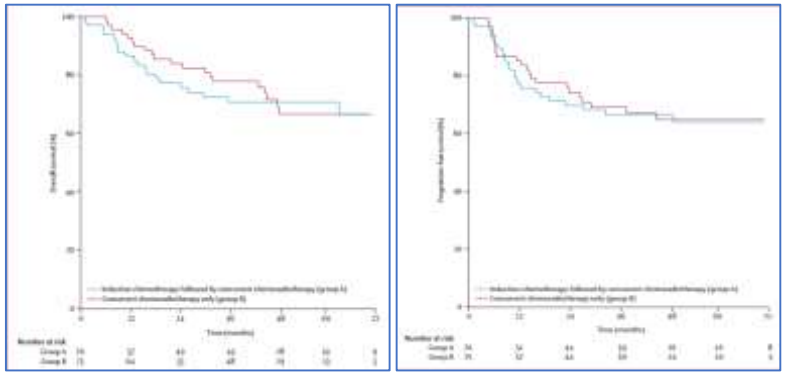
Cisplatin and Fluorouracil Alone or with Docetaxel in Head and Neck Cancer



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cisplatin, Fluorouracil, and Docetaxel in Unresectable Head and Neck Cancer



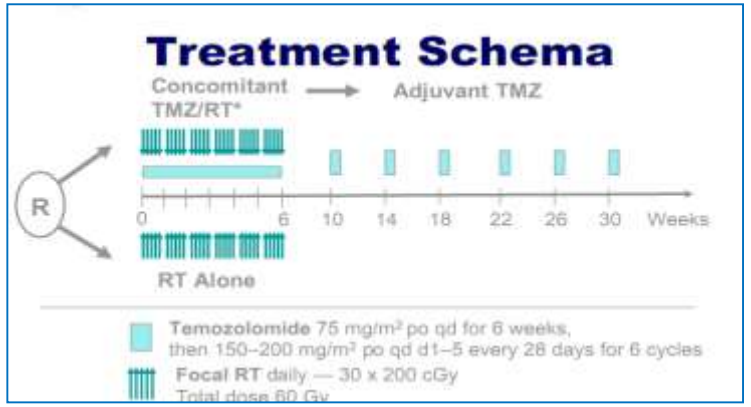
Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial

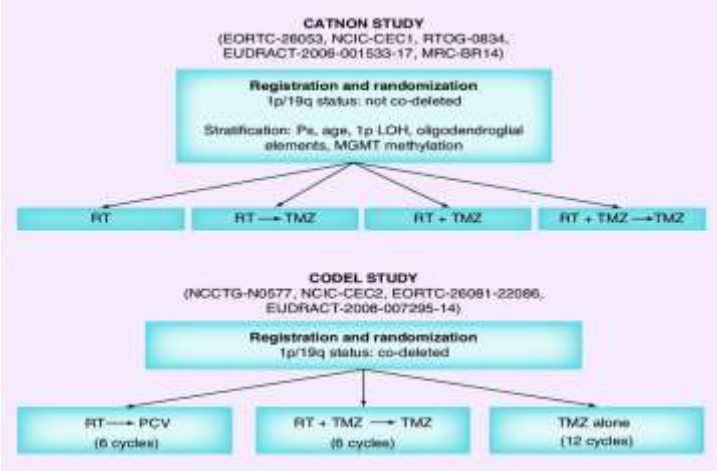
Robert Haddad, Anne O'Neill, Guilherme Rabinowits, Roy Tishler, Fadlo Khuri, Douglas Adkins, Joseph Clark, Nicholas Sarlis, Jochen Lorch, Jonathan J Beitler, Sewanti Limaye, Sarah Riley, Marshall Posner

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma





ONE ARM MUST BE: STANDARD OF CARE

Sample size calculation

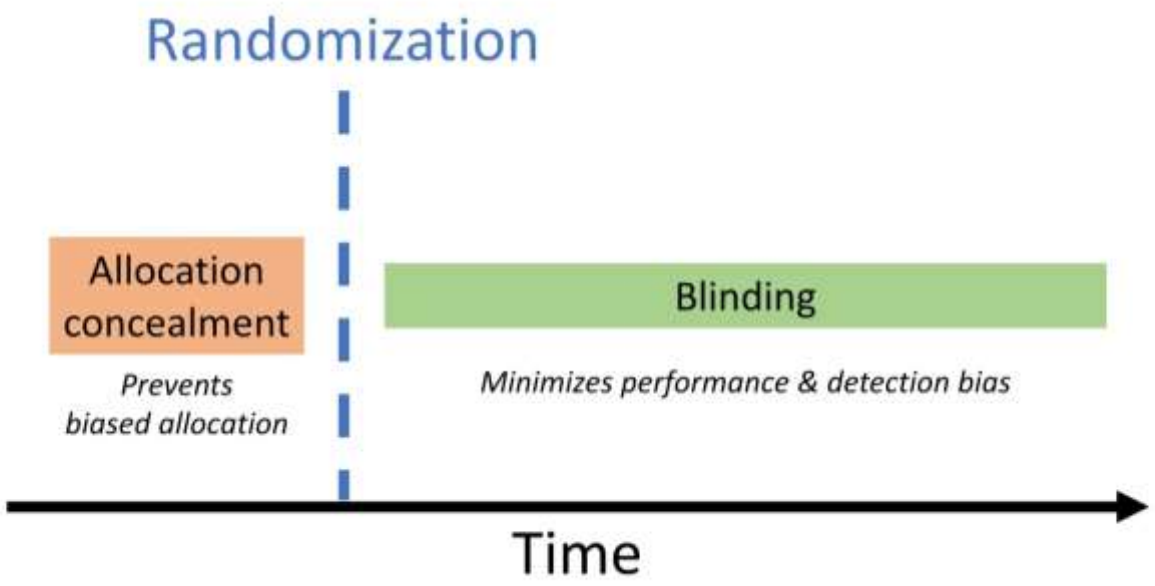
- The estimation of sample size along with other study related parameters depends on Type I error, Type II error and Power

- Type I error = (Reject H_0/H_0 is true).
- The probability of Type I error is called as level of significance (α)

- Type II error = (Accept H_0 / H_1 is true)
- Probability of type II error is denoted as β

Blinding

- Blinding, or "masking": Information that has the potential to influence study results is withheld from one or more parties



Interim analysis

- Analysis of data that is conducted before data collection has been completed
- Decision on the type of analyses to conduct
- Data and Safety Monitoring Boards (DSMBs)

Type of interim analysis	Explanation	Justification for use
Efficacy	• Early termination of a trial that is showing promising results • Control of type I error through group sequential methods or alpha-spending functions	• Usually for longer, larger studies and later phases of research • Ethical imperative for a promising treatment to reach the entire target clinical population
Futility	• Early termination of a trial that is not likely to achieve the intended objective (e.g., little chance of finding a "significant" treatment effect at the end of the study) • Employed through group sequential methods, error-spending functions, conditional power, or predictive power	• Reduces costs, resources, and patient burden for a trial with a low probability of "success" • Usually for mid-late-phase studies • Helpful in the context of recruitment and retention challenges
Safety	• Early termination (or pausing) of a trial for safety concerns • Should be coupled with efficacy analyses to evaluate the benefit-to-risk ratio	• Incorporated across all phases of research • Particularly important for vulnerable populations and high-risk interventions with more "serious" outcomes (e.g., death)
Sample size re-estimation	• Reassessment of the sample size required to ensure adequate power using updated information from interim trial data • Can be blinded or unblinded • May not necessarily spend alpha	• Allows for interim look at assumptions (standard deviations, event rates, correlations, etc.) • May be particularly useful for mid-late-phase studies

Ethical aspect

Respect for autonomy: We must not interfere with the decisions of competent adults, and also actively

Justice: All individuals should have an opportunity to participate in research unless contraindicated and we must not impose unfair burdens.

Beneficence: We must be fair and correct in all our actions and must take positive steps to prevent harm.

Non-maleficence: We must not harm others: "First, do no harm“, and wherever harm cannot be avoided, we must try to minimize the same.

Explores the scientific novelty, rationality and relevance

1.Justification for conducting the trial in the context of national priorities
2.Scientific merits of the research project and feasibility: Review of toxicological studies, laboratory and animal data
3.Technology transfer and capacity building at sites

Soundness of the study design:

Inclusion-exclusion criteria, Sample size,
Randomization/ blinding proceduresEnd-point assessment
Study procedures and follow-up schedulePharmacy plan

Informed consent document

- **Research Description**
- **Risk**
- **Benefits**
- **Alternatives**
- **Confidentiality**
- **Compensation**
- **Contacts**
- **Voluntary participation and withdrawal**

Consent is an appeal or invitation to participate in a research study in simple, easy to understand, local language

Signature of the participant and a witness not a part of the study team

Research methodology guideline

- Reference guidelines
  - Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement
  - ICH-GCP
- Reporting guidelines: Consolidated Standards of Reporting Trials (CONSORT)

- According to ICH E6 (R2):
  - A clinical trial protocol serves as a comprehensive document outlining
    - Objectives
    - Design
    - Methodology
    - Statistical considerations
    - Overall organization of a study

Data collection

Quality data collection

Statistics

- Poor p-value Interpretation: P-values do not provide direct information about the magnitude or clinical relevance of the effect
- Confidence intervals should always be reported to identify effect sizes that can be “ruled out”
- ITT principle is a fundamental concept in clinical trials but is frequently misunderstood. The ITT principle essentially states to “analyze as randomized, Not PP
- Missing data is one of the biggest threats to the integrity of a clinical trial
- Consider testing only important hypotheses to reduce the possibility of false conclusions
- Subgroup analyses should generally be considered exploratory analyses rather than confirmatory. It is advisable to pre-specify subgroup analyses to avoid “data dredging”
- Appropriate reporting of clinical trial results is crucial for scientific advancement. Selective reporting is very common and can result in sub-optimal patient care
- Bayesian statistics, allows calculation of the probability of a hypothesis being true given the data.

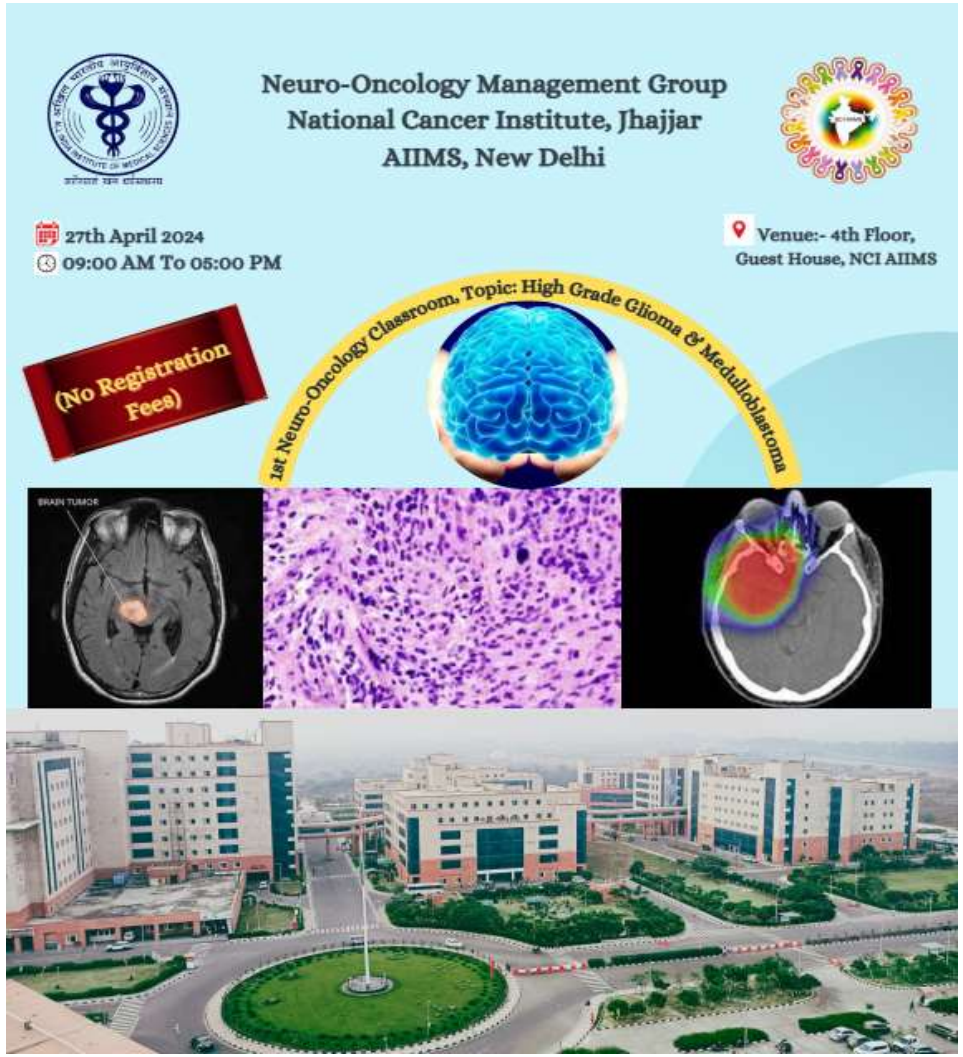
Building blocks for research

"**Building blocks**" encompass essential components

- Scientific methodology
- People-management skills
- Ethics and regulatory compliance
- Financial dynamics
- Participant recruitment
- Information technology and systems
- Institutional commitment

The entire process adheres to the comprehensive guidelines outlined by **EQUATOR**

Thank You



Upcoming course on Neuro-Oncology