Writing A Clinical Trial Protocol

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What is a clinical trial

A clinical trial tests potential interventions in humans to determine if the intervention represents an advancement and should be adopted for general use.

FDA 2003
Clinical Trials Test Research Hypothesis

- Good clinical trials test specific research hypothesis
- A hypothesis is a carefully formulated assumption developed in order to test its logical consequences
- An example: Adding TMZ to RT would improve outcomes in GBM
### Phases of Clinical Trials

<table>
<thead>
<tr>
<th>Phase</th>
<th>Number of Patients</th>
<th>Length</th>
<th>Purpose</th>
<th>% of Drugs Successfully Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>20 - 100</td>
<td>Several Months</td>
<td>Mainly safety</td>
<td>70%</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Up to several hundred</td>
<td>Several months to 2 years</td>
<td>Some short-term safety, but mainly effectiveness</td>
<td>33%</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Several hundred to several thousand</td>
<td>1 - 4 years</td>
<td>Safety, effectiveness, dosage</td>
<td>25% - 30%</td>
</tr>
</tbody>
</table>

For example, of 100 drugs for which investigational new drug applications are submitted to FDA, about 70% will successfully complete Phase 1 and go to phase 2, about 33% of the original 100 will complete phase 2 and go to phase 3; about 25-30% of the original 100 will clear phase 3 (and, on average, about 20 of the original 100 will ultimately be approved for marketing).
Evidence Based Medicine

EBM is the “conscientious and explicit use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from clinical research”

David Sackett
## Levels of Evidence

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Cochrane Systematic Reviews</th>
<th>Other SRs &amp; Meta-Analysis</th>
<th>Evidence Guidelines</th>
<th>Evidence Summaries</th>
<th>RCTs Case Cohorts, Control Studies</th>
<th>Clinical Research Critiques</th>
<th>Other Reviews of the Literature</th>
<th>Clinical Reference Texts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, A</td>
<td>Cochrane Database</td>
<td>ClinicalEvidence</td>
<td>DARE</td>
<td>ACP Journal Club</td>
<td>POEMS</td>
<td>USPSTF</td>
<td>National Guidelines</td>
<td>Textbooks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clearinghouse</td>
<td></td>
</tr>
<tr>
<td>5, C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Foraging Tools:**
  - Cochrane Database
  - ClinicalEvidence
  - DARE
  - ACP Journal Club
  - POEMS
  - USPSTF
  - National Guidelines Clearinghouse
  - Textbooks

- **Hunting Tools IN:**
  - InfoRetriever
  - Wiley
  - DynaMed
Clinical Trial Protocol

A clinical trial is an experiment to discover something about the real world

...... how people respond to clinical treatment

Clinical Trial Protocol is the window we construct to look at the world

...... a statement of the design of the clinical trial and how well it will be managed
Research Hypothesis and Protocol

*Research is only as good as protocol*

- Quality of research also depends on quality of proposal writing
- Must convince readers that the research idea is important
- Must provide evidence of sound methodology
- Must convince readers that you have a good grasp of relevant literature and major issues
- Must convince readers that you are competent and committed
Writing A Clinical Trial Protocol

WHY

WHEN

WHAT

HOW
WHY

- Compulsory pre-publication registration of clinical trials
- Competitive Funding: NCI, NIH, ICMR, DBT, DST
- Fulfill institutional mandate/obligations
- Establish reputation in selected field
- Keep updated with current knowledge
- Further enhance and enrich clinical practice

WHEN

- Whenever possible...... as early in transition from trainee to faculty
- Well before time of intramural research grant allocation
WHAT

• State why question is important
• Start with what you know and have published on it
• Ensure preliminary data support hypothesis
• Ensure hypothesis is tested by your aims
• Give a glimpse of what you hope to build your research on

HOW

• Allow plenty of time - drafts, revisions
• Collaborate – don’t go alone
• Engage mentors and colleagues
• Seek advice and assistance wherever necessary
• Trust your instincts
Elements of an ideal clinical trial protocol

• Study Title
• Synopsis or study outline
• Background and Rationale
• Aims, Objectives, and Hypothesis
• Population & Setting
• Interventions
• Study design
• Outcomes and Measures
• Study Procedures
• Statistical considerations
• Informed Consent
• Feasibility
Study Title

The title should briefly and accurately describe study design and 3 components of a well-built clinical question advocated by proponents of EBM i.e. population, interventions, and outcomes.

A phase III randomized trial of concurrent plus adjuvant TMZ added to standard radiation versus radiation therapy alone in adult patients with newly diagnosed supra-tentorial GBM.
Synopsis or study outline

**Purpose**
- Provide a brief yet clear summary
- Help readers understand, discuss, and support

**Key readers**
- Peer reviewers and funding agencies
- Busy, knowledgeable, and pre-occupied
- Appraise feasibility, importance, science, and value

*Simplify as much as possible......

..... But not more than that

*Albert Einstein*
Background & Rationale

Background: what is already known....

- Problem
  - epidemiology, causes, effects
- Existing treatment
  - mechanisms, benefits, harms
- Proposed intervention
  - mechanisms, benefits, harms

Rationale: what is the reason for going ahead

- For the treatment
  - as above
- For the trial
  - pros and cons
Background & Rationale-TMZ + RT in GBM

**Background: what is already about GBM**

**Problem**
- common, disabling, poor survival

**Existing treatment**
- surgery + adjuvant RT

**Proposed intervention**
- concurrent + adjuvant TMZ

**Rationale: what is the reason for going ahead**

**For the new treatment**
- radiation sensitizer & cytotoxic

**For the trial**
- acceptable toxicity
Aims, Objectives, Hypothesis

Aim: What are we trying to achieve

Objective: What are we trying to determine

Hypothesis: What are we expecting to find
Background & Rationale-TMZ + RT in GBM

**Aim:** What are we trying to achieve

- Improve survival and QOL in patients with GBM

**Objective:** What are we trying to determine

- What are the effects on survival and QOL of adding TMZ to standard RT following surgery

**Hypothesis:** What are we expecting to find

- Adding TMZ in the concurrent and adjuvant setting improves survival and QOL in GBM
Population - TMZ + RT in GBM

**Target**  
*Who are we trying to help*

Adult patients with supratentorial GBM planned for RT following maximal safe resection

**Inclusion**  
*Must haves..... (yes, yes, yes, yes)*

Histology, site, age with limits, PS with minimum value

Investigations includng CT/MRI and lab findings

**Exclusion**  
*Must not haves...... (no, no, no)*

Previous history of cancer or recurrent disease

Prior RT or chemo

Poor organ function precluding TMZ

Pregnancy or lactating women
Interventions – TMZ + RT in GBM

**Nature**
What is TMZ
A synthetic alkylating agent

**Administration**
How is it given
PO as 75/m2 daily concurrently during RT
PO as 200 mg/m2 D1-D5, q 4 weekly X 6 #

**Toxicity**
Myelosuppression, nausea, vomiting

**Co-medications**
Cotrimoxazole for PCP prophylaxis
Ondansetron as anti-emetic prophylaxis

**Control arm**
Standard RT alone
Study design – TMZ + RT in GBM
Should contain a simple flow diagram of the trial

Newly diagnosed GBM
stratification: age; Bx vs complete resection; ECOG PS 0,1 vs 2; institution

TMZ 200 mg/m² od x 5 day repeat every 28 days
x 6 cycles

TMZ 75mg/m² od x 6-7 wks

Focal Radiotherapy (60 Gy)
Tumour volume with 2-3 cm margin

Randomized controlled phase III,
open label, parallel group trial
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Consequence of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change in survival</td>
</tr>
<tr>
<td></td>
<td>Change in QOL</td>
</tr>
<tr>
<td>Outcome Measure</td>
<td>How the outcome is measured</td>
</tr>
<tr>
<td></td>
<td>Time to event for survival</td>
</tr>
<tr>
<td></td>
<td>QOL assessment at specified time points</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Ultimate event, characteristic, or criterion</td>
</tr>
<tr>
<td></td>
<td>OS, PFS, TTP, QOL score</td>
</tr>
<tr>
<td>Measure of effect</td>
<td>Ways of summarising and comparing</td>
</tr>
<tr>
<td></td>
<td>Difference in survival and QOL</td>
</tr>
</tbody>
</table>
Outcome measures & Endpoints – TMZ + RT in GBM

**Primary**
- Overall survival

**Secondary**
- Progression free survival
- Time to progression
- HR QOL
  - NPS & KPS
  - EORTC QLQ C 30 & BCM 20
  - FACT Br
- Steroid requirements
- Acute & late toxicity
One Most Important Thing

*The primary outcome of interest*

- Most compelling - should convince the sceptics
- Most reliable - results often conflicting
- Should determine sample size
- Influence all aspects of design
- Robust, transparent, and valid

Outcomes. Hypothesis, and Objectives should correspond
Study Procedures- what happens when

• Eligibility screen
• Baseline assessments
  Clinical including detailed neurological examination
  Mandatory imaging studies - CT/ MRI
  Mandatory laboratory studies - CBC, Biochemistry
  Optional tests - MRS/PET/Biological correlatives
• Treatment toxicity assessment (RTOG, EORTC, NCI CTC criteria)
• Response assessment (WHO, RECIST criteria)
• Follow up frequency and assessment
Radiation therapy specifications - TMZ + RT in GBM

• Radiation treatment
  permitted interval between surgery and RT start: 4-6 weeks
  time-relationship between TMZ and RT: 15-30 min

• Patient positioning & immobilization devices
  supine on appropriate neck rest with thermoplastic mask

• Patient data acquisition
  CT/MRI/surgical notes
  simulator based and or CT based planning

• Volumes of interest in terms of patient anatomy (ICRU 50 & 62)
  GTV, CTV, PTV
  OARs
Radiation Therapy Specifications

- Treatment technique
  - Conventional - SSD, SAD
  - Conformal - 3D CRT, SCRT, IMRT
- Field shaping, blocks, boluses to be pre-specified
- Dose computation
  - Conventional - In plane through the beam axes
  - Conformal - 3D planning algorithms (TPS)
- Equipment & Modality
  - Cobalt or LINAC
  - Photons, Electrons (specify energy)
  - Brachytherapy if any
Dose Prescription, Recording, & Reporting

Dose specification should be to the prescription point usually the isocentre (ICRU reference point)

- Prescription point dose
- Minimum and maximum (area of 2 cm²) dose in PTV
- Hot spot dose outside the PTV
- Doses to OARs
- Average dose in the PTV and its SD
- Conformity Index and Homogeneity Index (high-precision RT)
Radiation Therapy Specifications

- Tissue inhomogeneity considerations: lung, air, bone
- Modifications for age or field sizes: dose or dose per fraction reduction
- Dose homogeneity and off-axes reference points: -5% to +7%
- Permitted methods of dose compensation: wedges, blocks, compensators
- Fractionation schedule
  
  - Dose per fraction: 2 Gy/#
  - Number of fractions per day: 1 per day
  - RT number of days per week: 5 days
  - Total number of fractions: 30 #
  - Maximum allowed OTT: 6-7 weeks
  - Total dose: 60 Gy/30# 6 weeks
- Biological Isoeffect Dose if applicable
Radiation Therapy QA procedures

• Treatment verification
  Simulator films, Portal films: Frequency, Intervention

• Equipment specific
  Comparison of ionization chambers
  Beam calibration (as per specified protocol)
  Absorbed dose determination at specified points
  Measurement of dose homogeneity
  Mechanical checks (simulator, cobalt, LINAC)
  Calculation countercheck for treatment time or MU

• In vivo dosimetry (if part of multicentric study)
  Mailed TLD programmes
  MOSFET
Statistical Considerations

Sample size
how many

Difference worth detecting
what are we looking for

Power
how likely are we to find it

Confidence Intervals
how sure will we be

Accrual & Follow-up duration
how long will it take

Analysis plan
dealing with the expected

Describing or testing

Attrition

Missing values

Multiple comparisons
Statistical Plan – TMZ + RT in GBM

• Pick one primary endpoint: 2-year overall survival
• Specify the smallest difference worth detecting: 10%
• Specify standard primary analysis plan: Intent-to-treat
  
  Computer randomization
  
  Stratification on known prognostic factors
  
  Kaplan-Meier method for survival analysis

• Specify secondary analyses: as per protocol

280 patients per group provides an 80% power to detect a 10% improvement in 2-year overall survival at p=0.05
Ethical Considerations

Ethical Research = Good Science + Subject Protection

Obligations of Clinical Researchers To

- Patients (research subjects)
- Society
- Funding agencies
- Professional colleagues

The purpose of Informed Consent

- To provide information
- To facilitate decision-making
- To ensure understanding

It is a process not a document
Informed Consent - Contents

• Study involves research
• Purpose, duration, requirements
• Experimental procedures
• Comparison to standard treatment
• Special elements – randomization, stratification
• Risks and Benefits
• Alternatives to participation
• Confidentiality of data
• Compensation
• Contacts
• Statement of voluntary participation
• Conflicts of Interest
Feasibility

How would you overcome predictable barriers

Getting enough

Patients

Centres

Interventions

Finances
The Role of Organizational Intelligence: Business Process Flow

Integrate
- Provide centralized access
- Determine clinical trial results

Regulatory
- Support all activities within a compliance-enabling system
- Explore your research data

Compliance
- Evaluate safety and efficacy on a per-trial or across trials basis

Analyze

Discover
- Find hidden opportunities within the body of knowledge you've already built

Bring all associated research information together in one location.
Useful Websites for Clinical Trials & Scientific Writing

• ICMJE: www.icmje.org

• Consolidated Standards of Reporting Clinical Trial (CONSORT):
  www.consort_statement.org/revisedstatement.htm

• Epidemiologic studies: www.epidem.com


• JAMA: www.jama-ama-assn.org/issues

• Cochrane collaboration: www.cochrane.org/cochrane/revman.htm

• Cancer.gov (gateway to NCI websites): www.cancer.gov

• Cancer Trials Support Unit: www.ctsu.org

• Physician’s Desk Query: www.cancer.gov/cancerinfo/pdq

• ISRCTN: www.controlled-trials.com
Listening maketh ...... A wise man

Reading ..... A wiser man

Writing..... The wisest one