

Writing A Clinical Trial Protocol

Dr Tejpal Gupta, MD, DNB, PDCR

Assistant Professor, Radiation Oncology

Tata Memorial Centre



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

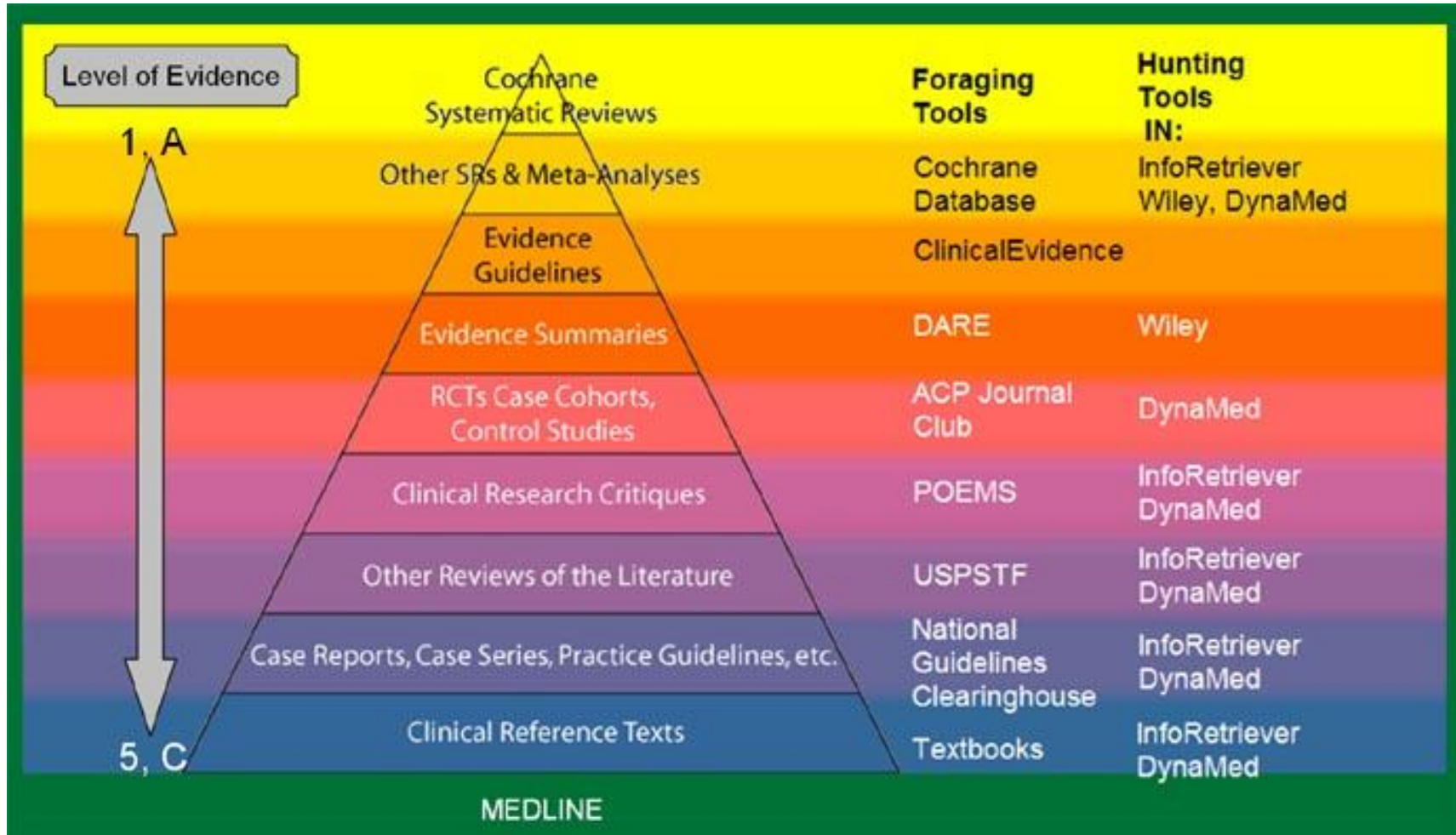
Testing in Humans				
	Number of Patients	Length	Purpose	% of Drugs Successfully Tested
Phase 1	20 – 100	Several Months	Mainly safety	70%
Phase 2	Up to several hundred	Several months to 2 years	Some short-term safety, but mainly effectiveness	33%
Phase 3	Several hundred to several thousand	1 – 4 years	Safety, effectiveness, dosage	25% – 30%
<p>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 20-30% of the original 100 will clear phase 3 (and, on average, about 20 of the original 100 will ultimately be approved for marketing).</p>				

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



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

General

Objective: What are we trying to determine



Hypothesis: What are we expecting to find

Specific

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

GENERAL



SPECIFIC

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 have..... (yes, yes, yes, yes)

**Histology, site, age with limits, PS with minimum value
Investigations including CT/MRI and lab findings**

Exclusion

Must not have..... (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-medication

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***

Outcomes of interest – TMZ + RT in GBM

Outcome

Consequence of interest

Change in survival

Change in QOL

Outcome Measure

How the outcome is measured

Time to event for survival

QOL assessment at specified time points

Endpoint

Ultimate event, characteristic, or criterion

OS, PFS, TTP, QOL score

Measure of effect

Ways of summarising and comparing

Difference in survival and QOL

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 - 3 D planning algorithms (TPS)**

- **Equipment & Modality**

 - Cobalt or LINAC**

 - Photons, Electrons (specifiy 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

Bring all associated research information together in one location.



Assess safety and efficacy on a per-trial basis, or across trials.

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

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
- BMJ resources: “Scientific writing: easy when you know how” BMJ Books 2002: www.bmjbooks.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