Writing A Clinical Trial Protocol

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SERVICE RESEARCH EDUCATION

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%

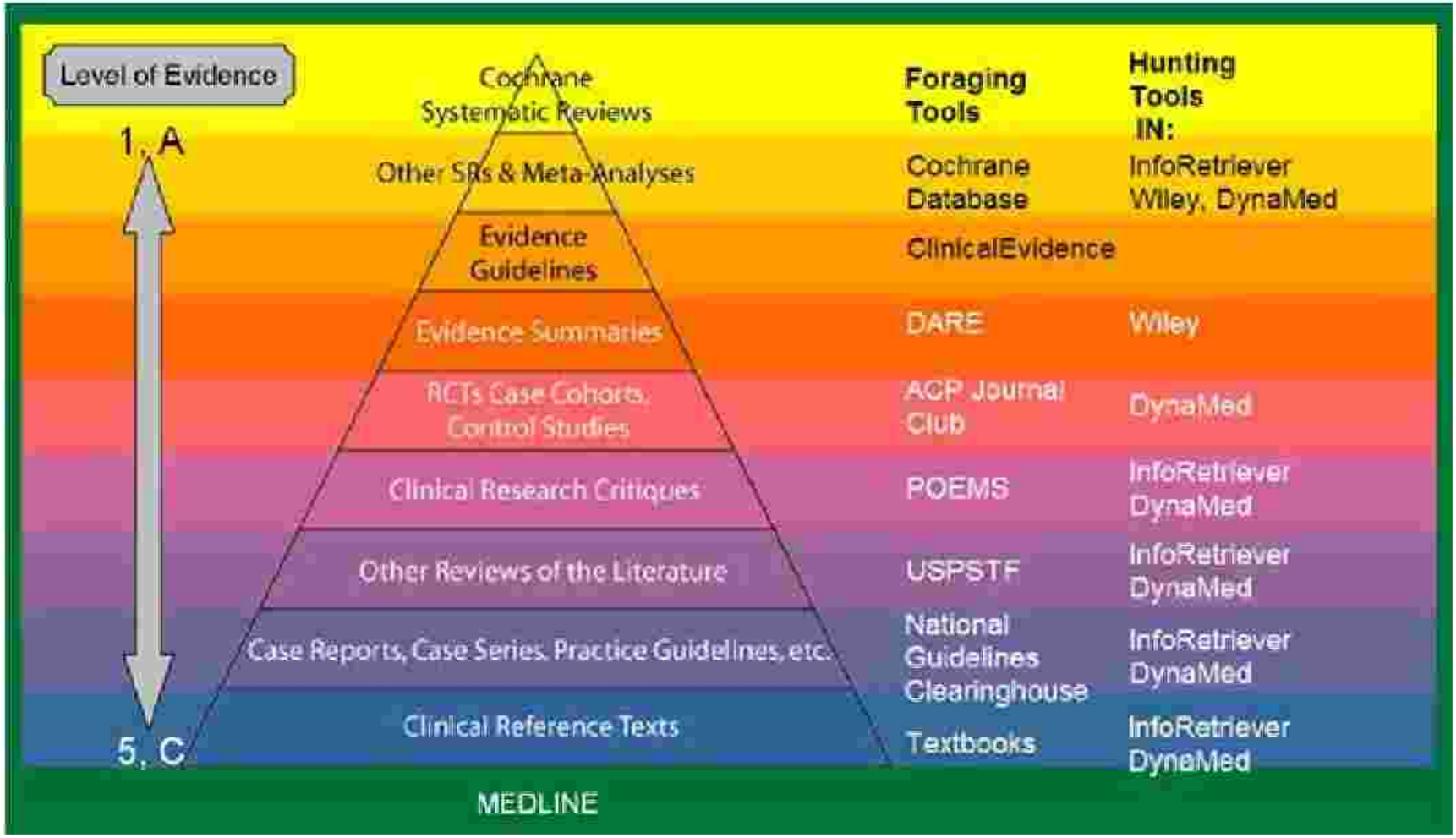
For example, of 100 drugs for which investigational new drug applications are submitted to FDA, about 70% will successfully complete Phase 1 and go to phase 2; about 33% of the original 100 will complete phase 2 and go to phase 3; about 25-30% of the original 100 will clear phase 3 (and, on average,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



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
- Collabotare – 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

General

Specific

Background & Rationale-TMZ + RT in GBM

GENERAL

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

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 haves….. (yes, yes, yes, yes)***

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

Investigations incluidng 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-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

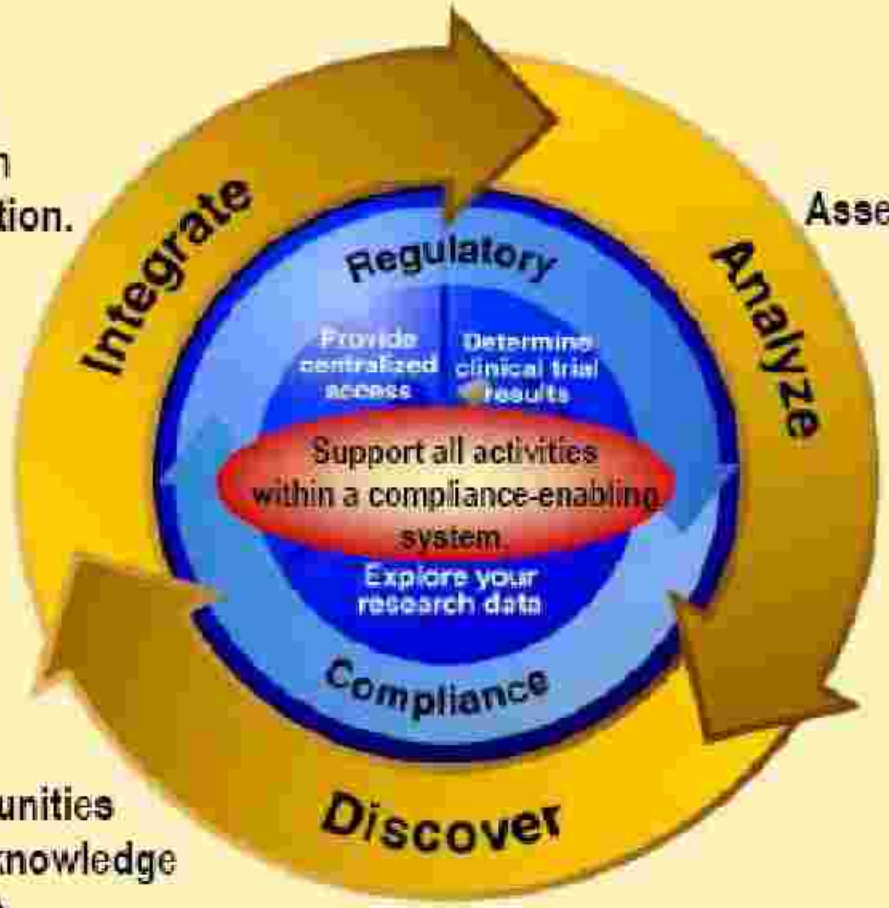
How would you overcome predictable barriers

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_statment.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