Filling in the Blanks: Core Elements of a Clinical Research Protocol

INS/OUTS OF PROTOCOLS: LANGUAGE/VOCABULARY

Clinical Trial Methods Course in Neurology
Saturday July 21, 2012

Jaishri Blakeley, MD and Alex Valadka, MD
Johns Hopkins University
Baylor College of Medicine

Disclosures

- Non-salary research support:
  - GlaxoSmithKline
  - Sanofi-Adventis
  - Lily
  - NCI: Cancer Therapeutic Evaluation Program
- Advisory Boards
  - Novartis: uncompensated
- Much of the content in this review is adapted from:
  - http://www.ninds.nih.gov/research/clinical_research/toolkit/protocoltemplate.html
  - http://www.nidcr.nih.gov/clinicaltrials/toolkitclinicalresearchers/clinicaltrialsprotocoltemplate/

Objectives

- Review the common and key elements to a clinical therapeutic protocol
- Introduce common protocol vocabulary
- Review protocol architecture and rationale

Core Assumption

- Research involving human subjects and an intervention
  - *"drug, device, therapy or process under investigation in a clinical trial which has an effect on outcome of interest in a study"*

Core Resources

- http://www.ninds.nih.gov/research/clinical_research/toolkit/protocoltemplate.html
- http://www.nidcr.nih.gov/clinicaltrials/toolkitclinicalresearchers/clinicaltrialsprotocoltemplate/

Purpose of a Protocol

- General principle:
  - This is your reference guide, instruction manual, dispute resolution tool –
    - Need to know where to find the data
    - Need clarity
    - Need consistency
  - If you are working with a group it is helpful to have the protocol architecture to be as similar as possible trial to trial

1. Title Page

Required

- Title
- Protocol number(s)
- Principal investigator and contact info
- Draft or Version number:
  - Make sure the header of every page of the protocol has the same date and version as the title page
- Date

Optional

- Funding mechanism
- Other support
- IND sponsor
- Institute program official
- Institute medical monitor
- Statement of compliance
  - Harmonization with Good Clinical Practice
    - Attest to compliance with the appropriate ICH codes; terms of the grant award for the project
  - Statement that all key personnel are in good standing re: Human Subjects Training
- Signature page
- List of key personnel and contact information

2. Table of contents & subsections

- Protocols are divided into major and minor sections to help quickly identify the needed information

3. Precis/Summary Page

Background

Patients with neurofibromatosis type 2 (NF2) develop tumors of the central and peripheral nervous system, including vestibular schwannomas, meningiomas, and ependymomas. Bilateral vestibular schwannomas (VSs) are the hallmark of NF2. As these tumors enlarge, they cause sensorineural hearing loss and, ultimately, complete deafness. Vestibular schwannomas demonstrate an angiogenic pattern of vasculature with increased microvascular density and size. Bevacizumab is a humanized IgG1 monoclonal antibody that binds all biologically active isoforms of human vascular endothelial growth factor (VEGF) with high affinity. This study will assess if bevacizumab will result in significantly improved hearing

Objectives

•PRIMARY OBJECTIVE: To determine the proportion of patients with hearing improvement with bevacizumab in patients with progressive hearing loss due to VS as assessed by word recognition scores.

•SECONDARY OBJECTIVES:

•To determine the proportion of patients with radiographic improvement (decrease in VS volume by ≥20%) in VS with bevacizumab.

•To assess the safety and tolerability of bevacizumab 7.5mg/kg every 3 weeks for 12 months in patients with NF2 and progressive hearing loss.

•To explore the durability of response in both hearing and decreased tumor volume.

• To explore the biological effects of bevacizumab by measuring: perfusion, permeability and vessel diameter using MRI tools including dynamic contrast enhanced (DCE) and apparent diffusion coefficient (ADC) measurements. levels of circulating endothelial cells (CECs), and plasma proteins (VEGF-A, VEGF-C, sVEGFR1, sVEGFR2, sVEGFR3, Col IV, SDF1a, IL-1beta, IL-6, IL-8, TNFalpha, G-CSF, Ang1, Ang2, sTie2, s-cKIT)

•To explore patient motivations and expectations for participation in a therapeutic trial for NF2

•To explore the impact of bevacizumab therapy on health and hearing related quality of life (QOL) measures.

Eligibility

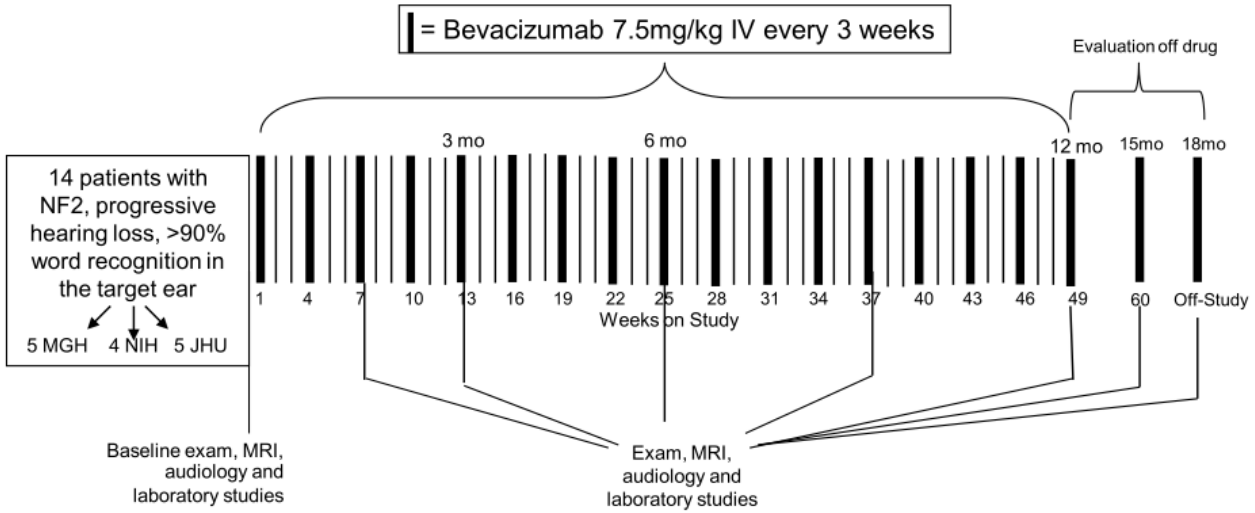
Adult and pediatric patients (12 years and older) with NF2 and evidence of active disease, defined as progressive hearing loss (with decrease in word recognition score) related to VS (i.e., not due to prior interventions such as surgery or radiation) in the preceding 24 months with a word recognition score of <90% in the affected ear that is confirmed with study-specific audiometry testing. Patients with a progressive VS affecting their only hearing ear are considered particularly appropriate study candidates.

Design

Bevacizumab will be administered intravenously at a dose of 7.5 mg/kg every three weeks (6 weeks = 1 treatment cycle).

Response will be evaluated using the primary endpoint of hearing response (defined as exceeding the 95% critical difference for word recognition score) at 3-month intervals.

4. Schema (optional, but helpful)



Phase II Study of IMC-1121B in Recurrent Glioblastoma Multiforme
PI: Jaishri Blakeley

Eligibility

≥18 years of age

Confirmed GBM with evidence of progression or recurrence on MRI after standard therapy

Measurable disease

KPS >60

Able to give informed consent

No limit on prior therapies, but no prior VEGF or PDGF therapy

No anticoagulation or blood clot, no uncontrolled HTN

>28 days from surgery

Endpoints

Primary: PFS-6 mo

Secondary: Radiographic response (ORR: CR + PR)
Tolerability
Durability of response
Corollary studies

Eligibility screening and informed consent

44 patients to get IMC-1121B 8 mg/kg IV every 2 weeks

MRI evaluation after 1st 2 cycles, then MRI q2 mo (every 4 cycles)

Continue IMC-1121B until evidence of progression or toxicity

5. Objectives

- Stating the main hypothesis the study seeks to address
  - Primary
    - MUST match the statistical section
    - Should be clearly stated and based on a clear hypothesis (by which you have established your null and alternative hypotheses for the statistical plan)
  - Secondary
    - Things you are interested in
      - Could support or expand upon the primary objective; could be exploratory
- **Concise and precise**
  - The primary endpoint defines almost everything else in your study. It has to be specific and consistent throughout the protocol.

6. Introduction

- Background Information
  - State the problem/need motivating the study
  - Give an overview of the field pertinent to the study
- Scientific rationale for this intervention
  - Educate your readers (members of the IRB, grant review committee, etc)
    - Should read like a good review paper
  - Information about the study intervention
    - Define the intervention (the drug, the exercise, etc.)
    - Potential risks
    - Potential benefits

7. Study Design

- Essentially the treatment plan
  - For the primary objective and any secondary objectives
    - *In order to address XX we will do YY at time point Z*
      - Do this for each of your objectives
  - Dosing, schedule, route, concomitant medications
  - Duration of intervention
  - Duration of follow-up

8. SELECTION AND ENROLLMENT OF SUBJECTS

- Inclusion criteria
  - Define the target population
    - Diagnosed by what criteria
    - With what clinical features
- Exclusion criteria
  - Spell out what you *specifically* need to exclude
    - i.e. must have normal liver function is different than bilirubin >2x institutional norms
- Art is to be specific enough to get a well defined patient population but not so specific that it is impossible to find an eligible patient

Example of inclusion criteria

- Eligibility:

1. Patients must have histologically proven supratentorial malignant glioma (anaplastic astrocytoma, anaplastic oliogodendroglioma or glioblastoma multiforme).
2. Patients must have received at least 80% of planned temozolomide and radiation therapy with no grade 3 or grade 4 toxicity attributed to the temozolomide.
3. Patients must have received planned treatment with radiation therapy and concomitant temozolomide at least 28 days but no more than 49 days prior to starting treatment on this study.
4. Patients must be at least 18 years of age.
5. Patients must have a Karnofsky Performance Status >60% (i.e. the patient must be able to care for himself/herself with occasional help from others).
6. Patients must have the following hematologic, renal and liver function:
   - Absolute neutrophil count > 1500/mm3, Platelets > 100,000/mm3, creatinine <1.7 mg/dl, total bilirubin ≤ 1.5 mg/dl, transaminases □4 times above the upper limits of the institutional normal.
7. Patients must be able to provide written informed consent.
8. Patients with the potential for pregnancy or impregnating their partner must agree to follow acceptable birth control methods to avoid conception. Women of childbearing potential must have a negative pregnancy test. The anti-proliferative activity of this experimental drug as well as the standard drug (temozolomide) may be harmful to the developing fetus or nursing infant.
9. Patients must have tumor tissue form completed and signed by a pathologist. See section 9.7 for details.

Example of exclusion criteria

- Ineligibility:

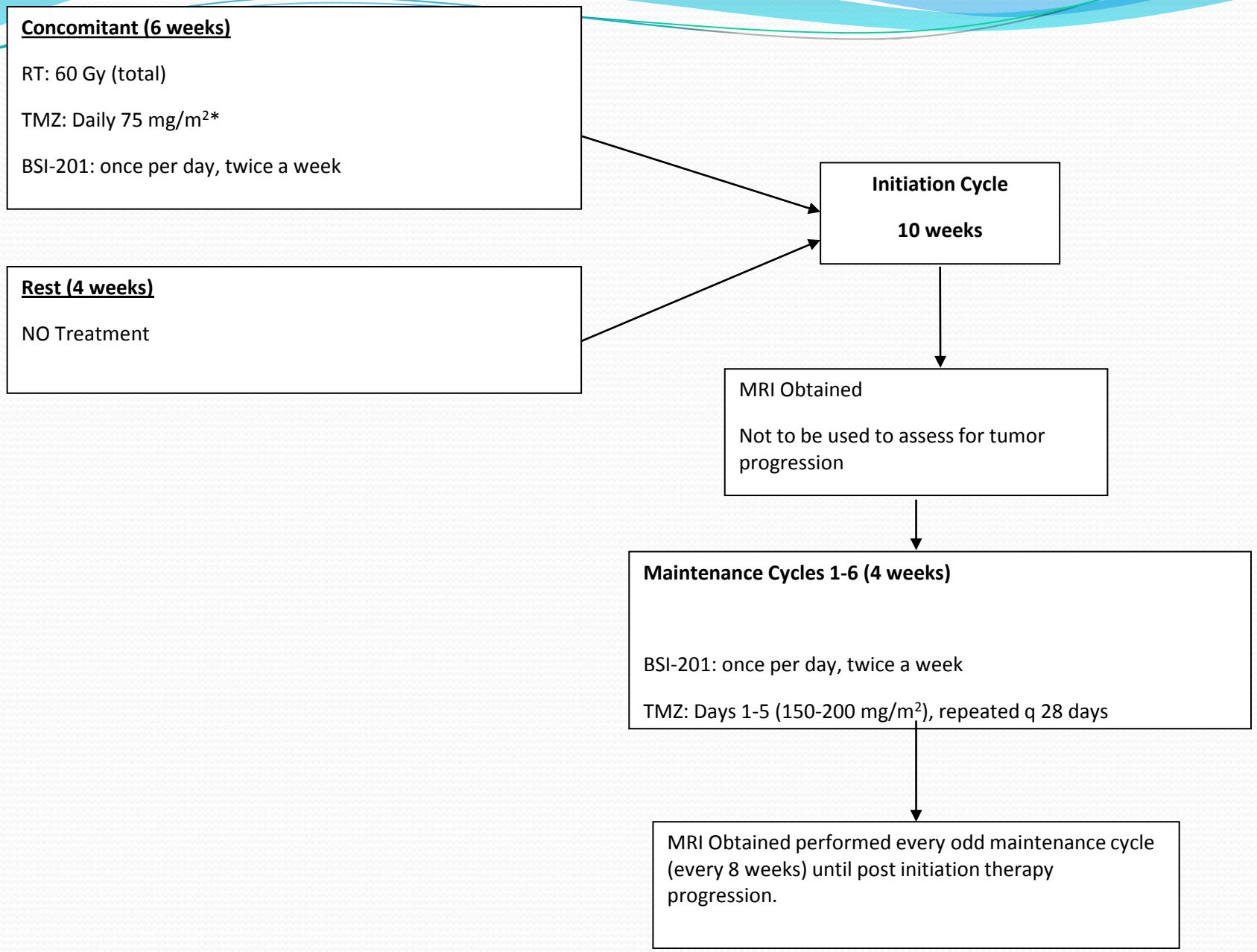
1. Patients with serious concurrent infection or medical illness, which would jeopardize the ability of the patient to receive the treatment outlined in this protocol with reasonable safety.
2. Patients who are pregnant or breast-feeding. The anti-proliferative activity of this experimental drug and temozolomide may be harmful to the developing fetus or nursing infant.
3. Patients receiving concurrent therapy for their tumor (i.e. hemotherapeutics or investigational agents).
4. Patients with a concurrent or prior malignancy are ineligible unless they are patients with curatively treated carcinoma-in-situ or basal cell carcinoma of the skin. Patients who have been free of disease (any prior malignancy) for ≥five years are eligible for this study.
5. Patients cannot be receiving cytochrome P450-inducing anticonvulsants (EIAEDs; *e.g.,* phenytoin, carbamazepine)

8. SELECTION AND ENROLLMENT OF SUBJECTS

- Study Enrollment Procedures
  - Describe the process for:
    - How patient will be identified and informed of the study
    - How patients will be screened
      - How this will all be recorded
    - Consent process
    - Process for subject assignment

9. Study Interventions

- Another place where a schema is helpful
- Intervention
  - What (drug, exercise), where (gym, clinic, ICU), when
    - All very specific
  - Foreseeable complications
    - Proposed interventions for complications
      - i.e. anti-nausea medications
- If using drug or tool, handling of drug or tool (accountability)
  - Enough detail, but not too much *(Operations Manual)*


Concomitant (6 weeks)
RT: 60 Gy (total)
TMZ: Daily 75 mg/m2*
BSI-201: once per day, twice a week
Rest (4 weeks)
NO Treatment
Initiation Cycle
10 weeks
MRI Obtained
Not to be used to assess for tumor progression
Maintenance Cycles 1-6 (4 weeks)
BSI-201: once per day, twice a week
TMZ: Days 1-5 (150-200 mg/m2), repeated q 28 days
MRI Obtained performed every odd maintenance cycle (every 8 weeks) until post initiation therapy progression.

9. Study Interventions

- Required interventions
  - *Must get 12mg drug every 3 weeks*
- Prohibited interventions
  - *Cannot start an enzyme inducing anti-epileptic drug*

10. Clinical and laboratory evaluations

	Baseline	Weekly (q 7 days)	Pre Odd cycles	Pre Even Cycles	Off Treatment (w/in 7 days of last dose)	Follow-Up
AE Evaluation		15	4	4	7,12	12
MRI	16		11		13	
H&P,Neuro exam	1		4		7	
Minimental	1		4		7	
KPS	1		4		7	
Vital Signs	1,5,6		4,6	4,6	6,7	
Hematology	1,9	2,8,9	4,8,9	4,8,9	7,9	
Serum Chemistry	1,10		4,10	4,10	7,10	
Serum Pregnancy Test	1					
Pharmacokinetics			17	17	17	
Laboratory correlative tissue sample	1,14					

10. Required observations

- Have to detail every test/measure that will be recorded
  - The timing (and window for the timing)
  - Reference to any required techniques
- Which measures are for screening and which are on-study evaluations
  - Special attention to on-study, off-study measures
- Specify how these measures will be documented
  - How they will be stored

11. Adverse Events

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).
- List expected and anticipated adverse events (alphabetically)
  - If using a drug there will be extensive pre-clinical or clinical data about the drug. This section should have a reasonable presentation of any known or predictable risks.
- Define the grading criteria of adverse events to be used
  - i.e. NCI Common Terminology Criteria for Adverse Events (CTCAE)
- Define whom AE will be reported to and in what time-frame
- State whom is eligible for adverse event reporting
  - i.e. all patients who get at least one dose of drug

11. Adverse Events

- List **required** versus **suggested** responses to adverse events
  - i.e. grade 3 hemorrhage: hold drug
  - i.e. grade 2 nausea, may use anti-emetic agents until resolution
- Define criteria for stopping treatment based on AE
- Define period of follow-up for patients who stopped treatment for AE
- Define records to be kept

12. Criteria for discontinuing intervention

- Reasons for coming off treatment
- Example of off treatment criteria:
  - Progression of Disease: Remove patient from protocol therapy at the time progressive disease is documented.
    - Disease progression is defined as: Progressive neurologic abnormalities not explained by causes unrelated to tumor progression (e.g. anticonvulsant or corticosteroid toxicity, electrolyte abnormalities, hyperglycemia, etc.) or a greater than 25% increase in the measurement of the tumor by MRI scan. If neurologic status deteriorates, on a stable or increasing dose of steroids, or if new lesions appear on serial MRI, further study treatment will be discontinued.
  - Extraordinary Medical Circumstance: If at any time the treating physician feels constraints of this protocol are detrimental to the patient's health remove the patient from protocol therapy.
  - Patient's refusal to continue treatment: In this event, document the reason(s) for withdrawal.
  - Failure to comply with protocol (as judged by the investigator such as compliance below 80%, failure to maintain appointments, etc.).
  - Patients who experience unacceptable toxicity.
- Plan for follow-up studies if treatment is stopped
  - Off-treatment versus off-study

13. Statistical Design

- Design:
  - General design issues pertaining to the primary objective (the hypothesis)
    - And to the secondary objectives
  - Statistical rationale for study design
  - Factors used for stratification
  - Description of methods and rationale for sample size

- Data Analysis
  - For primary and then all other objectives
    - Assumptions, anticipated confounding variables, plan for missing data points, poor enrollment, etc.

14. Data Monitoring and Reporting

- Records to be kept
  - For how long, where?
- Data management plan
  - Local versus multi-site study
    - Coordinating site responsibilities
    - Local site responsibilities and time-line
- Plan for Data sharing
  - Who will get data, when, how will it be identified/de-identified
- Quality Assurance
  - PI, CRO, DSMB
  - Schedule for audits

15. Protection of Human Subjects

- Regulatory oversight
  - Local (IRB)
  - National (FDA, Health and Human Services) or International
  - Sponsor

- Consent Process
  - Model consent as an appendix
    - Parameters re: use of proxy; waiver of consent