The Science of Drug Discovery:
The Intersection of Clinical Trials and Drug Development

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The Many Faces of Clinical Research

- Natural History Study
  - The impact of congenital cytomegalovirus infection on hearing
- Evaluation of a Diagnostic
- Assessment of an Intervention
  - Benefits of drug eluting stent placement
- Appraisal of a Drug
  - Placebo controlled
  - Drug – Drug Comparison
  - Open label evaluations
Who is the Sponsor?

- **Industry**
  - Goal is to license the intervention (make money)

- **An Academic Institution**
  - Goal is to generate new knowledge
  - Add value to intervention
  - Establish proof of principle

- **An Individual**
  - Goal is to establish proof of principle and value
  - Advance a career
Components of a Clinical Trial

- What hypothesis do you wish to test?
  - Grounded in a literature search
  - Outcome A exceeds Outcome B by what percent?
    - Usually 25-50% margin
  - Non-inferiority (within 10% variability)
  - Is it ethical?

- How does that translate to endpoints?
  - Primary
  - Secondary
  - Toxicity
  - Exploratory
First Steps

- Data Management Plan
  - Where will the data go?
  - How is verified?
  - How is it protected
- Biostatistical Design
  - Sample size
  - Randomization
  - Data Safety and Monitoring Board Reports
  - Analysis Plan
What Happens Behind the Scenes?

- Statistical Review
- Design of Case Record Forms
- Review Board Approvals
  - Institutional Review Board
    - UAB/SRI
    - Western Review Board
  - Conflict of Interest Review Board
  - Gene Therapy Review
- Universal IRB
- Investigator’s Brochure
The Protocol

- Background and Significance
- Approaches to the Problem
- Relevant Data
  - Cell and Animal Experiments
  - If a drug, adsorption, distribution, metabolism and excretion
  - Toxicity
- Endpoints
- Inclusion/Exclusion Criteria
- Details of Evaluation (when, where and what)
- Sample size determination, including statistical methodology
- Adverse Event Monitoring
- Literature Cited
- Appendices, including Case Record Forms
- Compiled Investigator Brochure
Institutional Review Boards

- Review Informed Consent versus Assent
  - Understandable to a teenager
  - Accurate and without bias
- Evaluate mechanism by which consent will be obtained
  - Equipose
  - Conflict of Interest
- Marginalized Study Populations
  - Children
  - Women
  - Under represented minorities
Conflict of Interest Review

- **Goal:** to insure that all parties have no vested interest in the outcome of the study
  - Financial
  - Non-monetary gifts in kind
- **Investigators as well as family members**
- ‘**Ghost Writing**’
- **Does the Institution have a conflict of interest** (i.e. hold a patent)?
Federal Approvals

- Is an IND required?
  - Performed within the state of origin (i.e. does not cross state lines)
  - NDA directed

- Registration of Federally funded clinical trials

- Compliance requires adherence to Code of Federal Regulations (CFR)
Funding

- Government
- Industry
- Foundation or Philanthropy
- Institution
  - Health Service Foundation
  - Departmental
Stages of Clinical Development

- Phase 0
- Phase I
- Phase II
- Phase III
- Phase IV
Phase 0 Clinical Trials

- Phase 0 clinical trials are intended to expedite the clinical evaluation of new molecular entities.

- An exploratory IND supports the performance of first-in-human testing of new investigational agents at subtherapeutic doses based on reduced manufacturing and toxicologic requirements (drug-target effects, PK, PD)
Phase I

- Goal: to define distribution and potential effects of intervention

- Phase IA
  - Pharmacokinetics and Toxicity in Normal Volunteers
  - Entails sequential blood draws and collection of select biologic fluids

- Phase IB
  - Pharmacokinetics, Pharmacodynamics and Toxicity in patients with disease
Figure 1 Schematic representation of the study design for Version 1.0 and Version 2.0.
Figure 2 Concentration-time curves of GCV following (a) oral VGCV administration and (b) i.v. GCV administration.
Median GCV Concentrations Following IV Dosing at Days 4 and 34
Median GCV Concentrations Following PO Dosing at Days 6, 35, and 36

GCV Concentration (mg/L)

Day 6
Day 35
Day 36

Time (h)
Ganciclovir Clearance vs. Age Following IV Dosing

Clearance vs. Age

\[ R^2 = 0.417 \]
\[ r = 0.65 \]
Figure 3 Observed (OBS) vs model-estimated (PRED) GCV concentrations following oral and i.v. dosing; line is line of identity.
Whole Blood Viral Load
Phase II

- **Goal**

- **Phase IIA**
  - Performed in target population
  - Proof of Principle
  - Usually three doses of medication
  - N=120-160 per cell

- **Phase IIB**
  - Performed in target population
  - Expanded sample size to guarantee Proof of Principle
Ganciclovir Evaluation in Congenital CMV
Conduct of Study

Congenital CMV (culture proven)
With CNS Involvement

Informed Consent

Ganciclovir vs. No Treatment x 42 days
12 mg/kg/day

Monitoring

Clinical/Virologic    Serology    Toxicity

Escape:
Hematologic, Renal, Liver Toxicity
Clinical Decline

Follow-up
(Months 6, 12, 24, 36, 48, and 60)
Study Endpoints

- **Primary Endpoint**
  - *Improved BSER by one gradation (or remains normal) between baseline and 6 month follow-up*
    - Biologic assessment (total ears)
    - Functional assessment (best ear)

- **Second Endpoint**
  - *Laboratory improvement by 2 weeks*
  - *Clinical improvement*
Change in Hearing Between Birth and 6 Months of Age

Ganciclovir Recipients

100%

Worse

Improved or Unchanged

P < 0.01

No Treatment Group

59%

41% †

† > 36.7 dB
Change in Hearing Between Birth and \( \geq 1 \) Year of Age

**Ganciclovir Recipients**

- **79%** Improved or Unchanged
- **21%*** Worse

* 25 dB

**No Treatment Group**

- **68%**† Worse
- **32%** Improved or Unchanged

† > 30.6 dB

\( P < 0.01 \)
Phase III

- **Goal: Registrational Trial**
  - Controlled and Randomized
  - Monitored by DSMB
  - Usually 900-1000 patients per arm

- Two required for licensure

- Results must be filed whether positive or negative

- FDA demands adequate numbers of volunteers to determine safety
Shingles Prevention Study

- A double-blind, placebo-controlled trial
- Oka/Merck VZV strain
- Live, attenuated vaccine
  - Median dose = 24,600 pfu (19K-60K)]
  - 18-fold greater than childhood vaccine
- Age of subjects (38,500 subjects)
  - 60-69 years = 20,750
  - $\geq$ 70 years = 17,800
  - $\geq$ 80 years = ~2500
Background - Endpoints

- **Burden of Illness (BOI)**
  - Sum of all severity of illness scores for each of two treatment groups - vaccinees and placebo recipients

- **Post-herpetic neuralgia (PHN)**
  - Significant pain (≥ 3 on ZBPI)
  - ≥90 days after rash onset

- **Herpes Zoster (incidence/1000/year)**
Shingles Prevention Study: Endpoints

Endpoints = BOI and PHN

Severity-of-illness (component of BOI)

- Measured severity of HZ pain with a validated method (ZBPI; scale = 0 to 10)
- Recorded severity at defined intervals
- Plotted severity vs time after rash onset
- Determined area under the curve
- Score = 0 if no HZ
HERPES ZOSTER

AUC of ZBPI Worst Pain Scores* over Time

Hypothetical Example of AUC for One Subject With HZ

Days Since Rash Onset

Worst Pain Score

0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190

First ZBPI Evaluation at Day 5
End of 1st AUC
Recurrent pain, 2nd AUC starts
End of 2nd AUC
End of Follow-up

* ZBPI per Coplan et al. The Journal of Pain 5:344-356, 2004
Shingles Prevention Study

- Subjects – 38,500 (17,800 = ≥70 years)
- Completed study = >95%
- Suspected HZ – 1308 (V=481; P=827)
- Confirmed HZ - 989 (V=322; P=662)

Diagnosis

- PCR = 93.3 – 93.5%
- Culture = 0.6 – 1.2%
- Clinical = 5.3 – 6.0%
Shingles Prevention Study: Efficacy

- **Burden Of Illness**
  - 61.1% (51.1 – 69.1%)

- **Post-Herpetic Neuralgia**
  - 66.5% (47.5 – 79%)

- **Incidence of Herpes Zoster**
  - 51.3% (44.2 – 57.6%)
Vaccination Reduces Herpes Zoster Incidence


Placebo: n=19,247
Zoster vaccine: n=19,254

Cumulative incidence of HZ (%)

Years of follow-up

Placebo
Zoster vaccine

$P < .001$

Placebo: n=19,247
Zoster vaccine: n=19,254
Vaccination Reduces PHN Incidence


Placebo: n=19,247
Zoster vaccine: n=19,254

Cumulative incidence of PHN (%)

Years of follow-up

Placebo: n=19,247
Zoster vaccine: n=19,254

P < .001
Role of the Data Safety and Monitoring Board

- Guarantee the well-being of volunteers who participate in the trial
- Interim analyses for efficacy or undue toxicity
  - Lan Demets
  - O’ Brien Fleming
- Monitor temporal changes in therapy to make sure the trial design remains contemporary and ethical
Phase IV

- **Goal**: Verification of Phase III data
- **Guarantee safety**
- **Usually a few thousand patients**
Outcome

- Hopefully, improved outcome of patient intervention
- At least further insight into the natural history of disease
- Results of negative studies must still be reported in the literature
- If no benefit, integrity in the results