Biostatistical Considerations in Oncology Clinical Trials (Part 1): Early Phase Trials

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## Disclosures

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<th>Manufacturer/provider of service</th>
<th>Relationship: honoraria, speakers’ bureau, grants, research support, stock, consultant, et cetera</th>
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<tbody>
<tr>
<td>1.</td>
<td>Eli Lilly</td>
<td>Honoraria</td>
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<td>2.</td>
<td>Pfizer</td>
<td>Honoraria</td>
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<td>3.</td>
<td>Roche</td>
<td>Honoraria</td>
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<td>4.</td>
<td>Celgene</td>
<td>Honoraria</td>
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<td>5.</td>
<td>Astra Zeneca</td>
<td>Honoraria</td>
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<td>6.</td>
<td>Novartis</td>
<td>Honoraria</td>
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Learning Objectives (for Part 1 and 2)

Introduction
• Planning a trial: PICOT
• Phases of trials
• Statistical inference

Early Phase Trials
• Some phase I trial considerations
  ➢ Rule-based versus model-based designs
• Some phase II trial considerations
  ➢ Screening for efficacy using umbrella and basket designs
  ➢ Frequentist versus Bayesian

Late Phase Trials
• Analysis of time-to-event outcome measures: understanding Kaplan-Meier and hazard ratios
• Results from hypothesis testing: understanding p-values
• Sample size for hypothesis testing: understanding significance level and power
• Non-inferiority trials: understanding non-inferiority margin
• Rare cancers
Key Elements of Clinical Trial Design

- Population
- Intervention
- Comparator
- Outcomes
- Time frame

Multidisciplinary team
Phases of Clinical Trials

Phase I: Dose-finding
- Early phase: Phase I/II
  - Aim: to find safe dose of a NEW treatment and understand toxicities

Phase II: Single arm
- Late phase: Randomised PII/III
  - Aim: to determine if NEW treatment has sufficient efficacy to be worthy of further investigation

Phase III: RCT
- Influence clinical practice
  - Aim: to provide sufficient evidence to potentially change clinical practice
Why Do We Need Statistics?

Population

Is NEW better than STANDARD?

TRUE difference ‘treatment effect’

Sample

NEW

STANDARD

Minimise uncertainty

OBSERVED difference ‘treatment effect’

Statistical Inference

Estimation

Best ‘guess’ at size of treatment effect and uncertainty

Hypothesis Testing

Do data prove beyond reasonable doubt that treatments differ?
**Rationale for Phase I Dose-Finding Trials**

**Standard Assumptions**
- Increase in dose → increase in toxicity → increase in activity
- Monotonicity

Define Dose-Limiting Toxicity (DLT)
Choose acceptable target DLT rate
Determine Maximum Tolerated Dose (MTD)

MTD is the dose at which \( p(\text{DLT}) = \text{target DLT rate} \)

20% is an “acceptable” DLT rate set as a trade-off to potential benefits to patients
Phase I Dose-Finding Trials: 
Traditional 3+3 Cohort Rule-Based Design

- Objective: to seek the Maximum Tolerated Dose (MTD) - minimum 6 pts treated at MTD
- Define a dose limiting toxicity (DLT)
- MTD = dose with ≤1/6 DLT where next highest dose has ≥2DLT
- Start on the lowest dose \( d_1 \)

**Diagram:***

- Give \( d_i \) to 3 subjects
  - 0 DLT: Proceed to \( d_{i+1} \)
  - 1 DLT: Give \( d_i \) to 3 more subjects
  - ≥2 DLT: STOP recommend \( d_{i-1} \) as MTD
- ≥1 DLT: STOP recommend \( d_{i-1} \) as MTD
Continual Reassessment Method (CRM) for Dose-Finding Trials

Review of 1,235 studies between 1991 and 2006. Only 17 (1.38%) used CRM
Modelling the Dose-Toxicity Relationship

- Select doses, $d_1,...,d_k$
- $P(\text{toxicity})$ - increasing function of dose & restricted to $0-1$

Family of Dose Toxicity Curves (1-parameter models)

Hyperbolic tangent

\[
F(dose, beta) = \left(\frac{\tanh(dose) + 1}{2}\right)^{\exp(beta)}
\]

Logistic Model

\[
F(dose, beta) = \frac{\exp(-3 + \exp(beta) \cdot dose)}{1 + \exp(-3 + \exp(beta) \cdot dose)}
\]
# Phase I Dose-Finding Trials: Rule-Based Versus Model-Based Designs

Christina Yap on behalf of MRC Network of Hubs for Trials Methodology Research Adaptive Design Working Group; A quick guide why not to use A+B Designs

<table>
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<tr>
<th></th>
<th>Rule-based designs</th>
<th>Model-based designs</th>
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<tr>
<td><strong>Target DLT</strong></td>
<td>unclear</td>
<td>clearly defined &amp; can be flexibly chosen</td>
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<tr>
<td><strong>Patients treated at the optimal dose</strong></td>
<td>(relatively) few</td>
<td>(relatively) many</td>
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<tr>
<td><strong>Patients treated at sub-therapeutic doses</strong></td>
<td>(relatively) many</td>
<td>(relatively) few</td>
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<tr>
<td><strong>Utilisation of available data</strong></td>
<td>poor</td>
<td>efficient</td>
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<tr>
<td><strong>Extension to more complex questions</strong></td>
<td>difficult and dubious</td>
<td>smooth and straightforward</td>
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<tr>
<td><strong>Deviations from the plan (e.g. other doses, different numbers of patients on a dose)</strong></td>
<td>hard or impossible to incorporate</td>
<td>easily accommodated</td>
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Screening Multiple Targeted Treatments Using Umbrella and Basket Trials

- Molecular drivers of different cancers are being discovered
- Drugs are being developed to target these molecular drivers
- Successful drug development will increase molecular classification of disease in order to stratify treatment
- Umbrella and basket trials are an efficient type of trial design that stratifies a population of patients into multiple strata and enables experimental drugs to be tested in each strata
- Basket and umbrella trials allow you to run multiple parallel trials within one protocol
Basket Trial: Single drug targeting a single molecular aberration carried in a variety of tumours (Kummar et al JNCI 2015)
Umbrella Trial: multiple drugs targeting multiple molecular aberrations (Kummar et al JNCI 2015)
Multi-drug, genetic-marker-directed, non-comparative, multi-centre, multi-arm phase II trial in non-small cell lung cancer

Chief Investigator: Gary Middleton
Chief Biostatistician: Lucinda Billingham
Lead Investigators: Sanjay Popat, Timothy A Yap, Yvonne Summers, James Spicer
Team at CRCTU: Joshua Savage, Dee Wherton, Kate Fitzpatrick-Ellis, Peter Fletcher, Ian Nutt
SMP2 Team at CRUK lead by Rowena Sharpe and Catrin Middleton
Trial Management Group chaired by Sanjay Popat
Pharma partners: Astra Zeneca, Pfizer, Mirati, Plexxicon
National Lung Matrix Trial: an example of an umbrella trial

Menis J, Hasan B, Besse B
New clinical research strategies in thoracic oncology: clinical trial design, adaptive, basket and umbrella trials, new endpoints and new evaluations of response
Eur Respir Rev 2014; 23: 367-378
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<td>B1: TSC1/2 mutation-NSCLC</td>
<td>2.7%</td>
<td>✓</td>
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<td>B2: LKB1 mutation/deletion-NSCLC</td>
<td>6.4%</td>
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<td>C1: Proficient Rb &amp; p16 loss-SCC</td>
<td>29.0%</td>
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<td>C2: Proficient Rb and p16 loss-ADC</td>
<td>19.6%</td>
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<td>C3: Proficient Rb &amp; CDK4 amp-NSCLC</td>
<td>7.0%</td>
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<td>C4: Proficient Rb &amp; CCND1 amp-NSCLC</td>
<td>7.3%</td>
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<td>C5: Proficient Rb, LKB1 mut/del with actKRAS/MAPK-NSCLC</td>
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<td>C6: Proficient Rb and KRAS mutation–ADC</td>
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<td>D1: Met amplified-NSCLC</td>
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<td>D2: ROS1 gene fusion-NSCLC</td>
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<td>E1: NF1 mutation-SCC</td>
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<td>E2: NF1 mutation-ADC</td>
<td>4.6%</td>
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<td>F3: PIK3/AKT deregulation-NSCLC</td>
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<td>F4: PTEN loss &amp; mutation-SCC</td>
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<td>✓</td>
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<td>G1: EGFR mutation &amp; T790M+-NSCLC</td>
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<td>✓</td>
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20 drug-biomarker cohorts
Single Arm Phase II Trial

Eligible Patients

NEW Treatment

Response rate

Single stage: A’Hern
Two-stage: Simon’s

Historical data / clinical experience of standard treatment

0%  p0: Lower Benchmark  p1: Upper Benchmark  100%
Standard Frequentist Design for Single Arm Phase II Trial

Example: A’Herns design

\[ p_0 = 30\%, \ p_1 = 50\% \]
\[ \alpha = 10\%, \ 1 - \beta = 80\% \]

Statistical design:
Require total of 30 patients
‘Go’ decision = 13/30 (43%) 

Problem: ‘Missing the point’ in the actual trial
e.g. 13/31 (42%)
or 12/29 (41%)
Bayesian Approach to Analysis

Data from trial on treatment effect
Prior probability distribution for treatment effect

×

Enables prior evidence or beliefs to be incorporated into the final estimate of the treatment effect

Posterior probability distribution for treatment effect

Enables direct probability statements to be made about treatment effects

Bayesian allows analysis to answer the REAL question

Classical: $p$-value = $p \left( \text{data} \mid \text{no treatment effect} \right)$
Bayesian: posterior $\rightarrow p \left( \text{treatment effect} \mid \text{data, prior} \right)$

Incorporating prior represents reality of interpreting trial data
Simple Bayesian Two-Stage PII Design: e.g. National Lung Matrix Trial

Primary outcome measure: objective response
θ: unknown true objective response rate

\[ P(\theta < 30\%) \geq 0.9 \] STOP early @ Interim

\[ P(\theta \geq 30\%) \geq 0.5 \] GO

\[ N = 15 \]

\[ N = 30 \]
Illustrating Bayesian Analysis in NLMT

Beta-Binomial conjugate analysis
Prior: $\theta \sim \text{Beta}(a_0, b_0)$
Posterior: $\theta | r, n \sim \text{Beta}(a_0 + r, b_0 + n - r)$

Interim analysis: $3/15 = 20\%$
Final analysis: $13/30 = 43\%$

$P(\theta < 30\%) = 0.75$
$P(\theta > 30\%) = 0.95$
Compelling Evidence From Single Case Studies / Clinical Experience

B Positron-Emission Tomographic Scans

Baseline
After 3.5 Wk
Compelling Evidence From Single Arm Trial Can Change Clinical Practice

Example: waterfall plot after targeted treatment (N=50)

Objective response rate = 72%
95%CI: 58% - 84%
The Role of Nonrandomized Trials in the Evaluation of Oncology Drugs

R Simon¹, GM Blumenthal², ML Rothenberg³, J Sommer⁴, SA Roberts⁵, DK Armstrong⁶, LM LaVange⁷ and R Pazdur³

Old Paradigm

New Paradigm

Randomization

Drug X → Clinically small PFS or OS

Control

Single-Arm

Targeted Therapy → Large ORR

Clinical Pharmacology and Therapeutics 2015
Summary

- **Phase I dose-finding trials** – model-based rather than rule-based
- **Single arm phase II trials** – Bayesian may be better option
- **Umbrella and basket trials** are an efficient design for screening multiple drugs for multiple targets in multiple populations
- **Precision medicine** aims to develop drugs that give the RIGHT drug to the RIGHT patient to target their specific molecular drivers and therefore should create dramatic and biologically plausible treatment effects
- Evidence from **early phase trials** may be sufficient to change clinical practice when treatment effects are so dramatic AND biologically plausible that they must be real
- Increasing molecular characterisation of cancer generates **rare populations** for clinical trials that challenge conventional statistical design
- **Frequentists** use only the study data in estimation whilst **Bayesians** incorporate prior information and estimate probability distributions for treatment effects
- Good trial question framed in terms of **PICOT** with supported by a multidisciplinary team
Further Reading

• Berry SM, Carlin BP, Lee JJ, Muller P; Bayesian Adaptive Methods for Clinical Trials; Chapman and Hall 2011
• Cheung YK; Dose Finding by the Continual Reassessment Method; Chapman and Hall 2011
• Julious S, Say-Beng T, Machin D; An Introduction to Statistics in Early Phase Trials; Wiley-Blackwell 2010
• Yap C, Billingham L, Craddock C, Cheung YK, O’Quigley J; Dose Transition Pathways: The missing link between complex dose-finding designs and simple decision-making. *Clinical Cancer Research* 2017