Dose-finding in malaria

A combination dose-escalation study using Bayesian logistic regression modeling (BLRM)

B Magnusson

19 May 2016
Outline

- Malaria – disease overview
- Program overview and context for dose finding
- Candidate phase 2b study design
- Dose escalation – methodology reminder
  - Safety metrics
  - Bayesian logistic regression model for combination modeling
  - Prior specification and derivation
- Implementing the design
  - Planning
  - Communication
  - Simulations
- Summary
Malaria

*Disease overview*

- Mosquito-borne infectious disease
  - Human cases date back to 2700 BC
  - Historically associated with “bad air” (*mala aria*) around marshes

- Once common in the US and southern Europe

- Now endemic in a “broad band” around the equator

- 2015 facts & figures (WHO)
  - 214 million cases worldwide
  - 438,000 documented deaths
  - 70% of deaths occur in children under 5 years old

- Treatment:
  - In late 19th century: mustard bath, kerosene massage, lots of whiskey
  - Current: artemisinin-based combination regimens (~95% cure rate)
Program overview

**Key question for phase 2b**

- **Setting:**
  - Investigational compound (drug A) under development for treatment of malaria
  - Preferred combination partner (drug B) has been identified

- **Phase 2a completed – monotherapy only**
  - Multiple-dose and single-dose regimens have been investigated
  - Potential for *single dose cure*

- **Key question for phase 2b – is single dose cure feasible?**
  - Components to answer question: need a combination dose with
    - satisfactory safety profile
    - efficacy comparable with existing multi-day regimens (~95% cure rate)

- In the context of malaria treatment, higher doses are preferable

- Primary purpose of dose-finding: establish the maximum tolerated dose (MTD)
Candidate design for phase 2b

- Candidate phase 2b design:
  - Consider dose escalation methodology often used in phase 1 oncology studies
  - Escalate separately for monotherapy and combination therapy
  - Note: partner drug dose kept constant

- Primary endpoint
  - Rate of occurrence of specific dose-limiting toxicities (DLTs)
  - DLTs are pre-defined according to known program and indication risks

- Components of dose escalation
  - Incorporate contextual information from previous studies
  - Quantify dose-toxicity relationship with BLRM
  - Provide model-based recommendation of the next dose level
Interim analysis algorithm

Inference → dose recommendations

- BLRM input – cumulative DLTs and sample size at each studied dose

- Inference:
  - Estimate dose-toxicity relationship
  - Derive safety metrics:
    - Under-dosing  DLT probability < 0.05
    - Target dosing  DLT probability between 0.05 and 0.20
    - Overdosing    DLT probability > 0.20
  - Report interval probability for each candidate dose

- Model-based dose recommendation:
  - Dose with high probability of being in target interval for DLT
  - AND maximal overdose probability of 0.25 (EWOC)
  - Possible recommendations: *escalate*, *repeat*, *de-escalate*
    or stop and declare MTD
Combination BLRM

Modeling the dose-toxicity relationship

\[
\log(\text{odds}(\pi_{1,d_1})) = \log(\alpha_1) + \beta_1 \log(d_1)
\]

\[
\log(\text{odds}(\pi_{2,d_2})) = \log(\alpha_2) + \beta_2 \log(d_2)
\]

\[
\pi_{12,d_1,d_2}^0 = \pi_{1,d_1} + \pi_{1,d_2} - \pi_{1,d_1} \pi_{2,d_2}
\]

\[
\text{odds}(\pi_{12,d_1,d_2}) = \text{odds}(\pi_{12,d_1,d_2}^0) \exp(\eta d_1 d_2)
\]

\[
(\alpha_1, \beta_1, \alpha_2, \beta_2 > 0)
\]

- (note: reference/scaling doses dropped in formulas)
- if no dose-dependent interaction desired: simply use \(\exp(\eta)\)
- no interaction \(\iff \eta = 0\)
- typically \(\eta > 0\), but not necessarily

Dose-toxicity relationship for each individual drug

DLT probability under no interaction

Dose-dependent interaction term on odds scale
Combination BLRM

Specifying the priors

MAP* prior for $\alpha^*$, $\beta^*$ obtained from hierarchical model

$$r_{d,h} \sim \text{Bin}(\pi_{d,h}, n_{d,h})$$

$$\log(\pi_{d,h} / (1 - \pi_{d,h})) = \log(\alpha_h) + \beta_h \log(\text{d}/\text{d}^\ast)$$

$$(\log(\alpha_h), \log(\beta_h)) \sim \text{BVN}(\mu_1, \mu_2, \psi)$$

$$(\log(\alpha^*), \log(\beta^*)) \sim \text{BVN}(\mu_1, \mu_2, \psi)$$

Priors

$$\psi = \begin{pmatrix} \tau_1^2 & \tau_1 \tau_2 \rho \\ \tau_1 \tau_2 \rho & \tau_2^2 \end{pmatrix}$$

$$\mu_1 \sim \text{N}(m_{\mu_1}, s_{\mu_1}^2), \mu_2 \sim \text{N}(m_{\mu_2}, s_{\mu_2}^2)$$

$$\tau_1 \sim \text{LN}(m_{\tau_1}, s_{\tau_1}^2), \tau_2 \sim \text{LN}(m_{\tau_2}, s_{\tau_2}^2), \rho \sim \text{Unif}(-1, 1)$$

Interaction prior – normal prior on $\eta$

$$\text{odds}(\pi_{12,d_1,d_2}) = \text{odds}(\pi^0_{12,d_1,d_2}) \exp(\eta d_1 d_2)$$

*Meta-analytic predictive
Deriving the MAP prior

- Contextual information from patient studies of drug A:
  - Two single-dose studies – several dose levels
  - One multiple-dose study – one dose level
    - Summed and treated as single dose in meta-analysis

- Differential discounting of historical information:
  - Assumption of \textit{multi-dose = single-dose x days} is crude, needs attention!
  - Approach: Split prior data into strata (single vs. multiple-dose)
  - ...and assume larger prior variability in multiple-dose stratum

- Deriving the MAP prior:
  - The described model can be easily fit with BUGS/JAGS/Stan...
  - Approximate MAP prior with bivariate normal mixture
  - Mixture components can be written directly in the protocol
Prior distributions for dose-toxicity

- **MAP prior fitted to the available dose-DLT data and robustified**
- **A priori: 25mg is MTD, 50mg too toxic, but substantial uncertainty**

Main source of information for drug B: **drug label**
- Single dose of drug B at recommended dose expected to be relatively safe

No dose-response data, so two assumptions for dose of interest:
- $\Pr(\text{DLT} < 0.2) = 0.95$ and $\Pr(\text{DLT} < 0.05) = 0.5$
- Converted into a bivariate normal prior to fit with the combination BLRM setup
Implementing the design

Planning, simulating, communicating!

- Many (though not all) members of clinical team were unfamiliar with this type of design

- Clear visual communication essential to ensure clarity regarding
  - Methodology – quantification of uncertainty in DLT rates
  - Credibility – sanity checks that reasonable recommendations will be made
  - End-to-end understanding – illustration of a hypothetical trial

- Robustness assessment – does the design perform as desired?

- Simulation plan written to
  - Define dose-toxicity scenarios for evaluation
  - Define metrics for comparison of competing design options
  - Agree on key design parameters such as sample size
    - In a cohort/overall
**First interim analysis**

_Dose recommendation_

- **Question:**
  - “Given all the assumptions for the prior...”
  - “…and given the agreed-upon limits for dose toxicity categories...”
  - “…does the design make reasonable recommendations in light of actual data?”

- **Address by showing grid of outcomes for first IA**

Assumptions:
- 25 patients per cohort
- Mono starting dose: 50mg
- Combo starting dose: 25mg
Example – Complete study

*Using maximal escalation rule*
# Cohort 1

**Monotherapy 2/25; Combination 1/25**

<table>
<thead>
<tr>
<th>Dose</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>100</th>
<th>125</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Patients</td>
<td>0</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td># DLT</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Patients</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td># DLT</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Monotherapy**

- Drug A dose
- DLT probability

**Combination**

- Drug A dose
- DLT probability

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**Bayes Pharma | B Magnusson | 19 May 2016 | Malaria dose escalation study | Business Use Only**
Cohort 1

Monotherapy 2/25; Combination 1/25

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<th>100</th>
<th>125</th>
</tr>
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<tbody>
<tr>
<td># Patients</td>
<td>0</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td># DLT</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Patients</td>
<td>25</td>
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<tr>
<td># DLT</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Both mono and comb may escalate, 75mg and 50mg respectively.

Drug A dose

Monotherapy

Combination

Overdose

Target dose

Under-dose
Cohort 2

Monotherapy 4/25; Combination 3/25

<table>
<thead>
<tr>
<th>Dose</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>100</th>
<th>125</th>
</tr>
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<td>Mono</td>
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<td>25</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td># DLT</td>
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<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comb</td>
<td># Patients</td>
<td>25</td>
<td>25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td># DLT</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Monotherapy**

**Combination**

![Monotherapy Graph](image1.png)

![Combination Graph](image2.png)
### Cohort 2

**Monotherapy 4/25; Combination 3/25**

<table>
<thead>
<tr>
<th>Dose</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>100</th>
<th>125</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>0</td>
<td>25</td>
<td>25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td># DLT</td>
<td>2</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># Patients</td>
<td>25</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td># DLT</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mono and comb should repeat 75mg and 50mg respectively, escalation not possible due to EWOC.

**Graphs:**

**Monotherapy**:
- Drug A dose: 25 to 200
- Probability: 0 to 0.5
- Dose levels: 25, 50, 75, 100, 125
- DLT: 0-0.2
- Target dose: 0.05-0.2
- Overdose: 0.2-1
- Under-dose: 0-0.05

**Combination**:
- Drug A dose: 25 to 200
- Probability: 0 to 0.5
- Dose levels: 25, 50, 75, 100, 125
- DLT: 0-0.2
- Target dose: 0.05-0.2
- Overdose: 0.2-1
- Under-dose: 0-0.05
Cohort 3

Monotherapy 2/25; Combination 2/25

<table>
<thead>
<tr>
<th>Dose</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>100</th>
<th>125</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>0</td>
<td>25</td>
<td>50</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td># DLT</td>
<td>2</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
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<tr>
<td># DLT</td>
<td>1</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Monotherapy**

**Combination**
Cohort 3

Monotherapy 2/25; Combination 2/25

Both mono and comb may escalate, 100mg and 75mg respectively

<table>
<thead>
<tr>
<th>Dose</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>100</th>
<th>125</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono</td>
<td># Patients</td>
<td>0</td>
<td>25</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td># DLT</td>
<td>2</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comb</td>
<td># Patients</td>
<td>25</td>
<td>50</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td># DLT</td>
<td>1</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overdose

Target dose

Under-dose

Drugs A dose

Probability

Monotherapy

Combination

0.2-1

0.2-1
## Cohort 4

**Monotherapy 6/25; Combination 3/25**

<table>
<thead>
<tr>
<th>Dose</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>100</th>
<th>125</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>0</td>
<td>25</td>
<td>50</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td># DLT</td>
<td>2</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| # Patients | 25 | 50 | 25 | 0 |
| # DLT | 1 | 5 | 3 | |

**Drug A dose**

### Monotherapy

![Graph for Monotherapy](image)

### Combination

![Graph for Combination](image)
**Cohort 4**

**Monotherapy 6/25; Combination 3/25**

<table>
<thead>
<tr>
<th>Dose</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>100</th>
<th>125</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>0</td>
<td>25</td>
<td>50</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td># DLT</td>
<td>2</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td># Patients</td>
<td>25</td>
<td>50</td>
<td>25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td># DLT</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Monotherapy MTD established = 75mg; Continue with combination therapy.

**Drug A dose**

- **Monotherapy**: Overdose at 100, 125, 150, and 200 mg; Target dose at 25, 50, and 75 mg; Under-dose at 0-0.05 mg.
- **Combination**: Overdose at 100, 125, 150, and 200 mg; Target dose at 25, 50, and 75 mg; Under-dose at 0-0.05 mg.
## Cohort 5  
*Combination 4/25*

<table>
<thead>
<tr>
<th>Dose</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>100</th>
<th>125</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>0</td>
<td>25</td>
<td>50</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td># DLT</td>
<td>2</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

| # Patients | 25 | 50 | 50 | 0 | 0 |
| # DLT | 1 | 5 | 7 | 0 | 0 |

### Monotherapy

![Graph showing DLT probability for monotherapy](image1)

**Drug A dose**

### Combination

![Graph showing DLT probability for combination](image2)

**Drug A dose**
**Cohort 5**

*Combination 4/25*

<table>
<thead>
<tr>
<th>Dose</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>100</th>
<th>125</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>0</td>
<td>25</td>
<td>50</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td># Patients</td>
<td>25</td>
<td>50</td>
<td>50</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td># DLT</td>
<td>1</td>
<td>5</td>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Combination MTD established = 50mg (75mg could also be chosen)

**Monotherapy**

**Combination**

Drug A dose vs. Probability

- **Monotherapy**: Dose escalation study
- **Combination**: Drug A dose with overdose, target dose, and under-dose conditions.

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Design evaluation

Simulating study operating characteristics

- A simulation plan was written in collaboration with the clinical team

- Key simulation parameters
  - Cohort size: 10, 20, 25, 30
  - Minimum number of patients enrolled: three cohorts
  - Maximum number of patients enrolled: eight cohorts
  - Minimum enrolled at the MTD combination: two cohorts

- Dose-toxicity scenarios:
  - Mild: 75 borderline under / 100 target / 125 over
  - Moderate 1: 75 target / 50 borderline under / 100 over
  - Moderate 2: 75 borderline over / 50 target
  - Toxic: 50 borderline over / 25 target
Design evaluation

Simulating study operating characteristics

- Metrics for evaluation:
  - Proportion of patients receiving target dose, overdose, and under dose
  - Probability of recommending a target dose, overdose, or an under dose as the MTD
  - Expected total sample size

- Simulations done with an internally developed library (R & JAGS)

- High-performance computing cluster for fast execution

- For simplicity, each arm (mono/comb) was simulated separately
  - Simulated OCs are thus likely “conservative” as the real trial will use information from both arms at each IA

- For each simulation configuration:
  - Summary of metrics – high-level check of OC and suitable for protocol
  - Detailed diagnostic plots – essential for fine-tuning of design parameters
Simulation output

High-level summary table

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metric I</td>
<td>57.83</td>
<td>Average proportion of patients in target dose region (&gt;= 5% - 20%)</td>
</tr>
<tr>
<td>Metric II</td>
<td>25.14</td>
<td>Average proportion of patients in over dose region (&gt;= 20%)</td>
</tr>
<tr>
<td>Metric III</td>
<td>17.03</td>
<td>Average proportion of patients in under dose region (&lt; 5%)</td>
</tr>
<tr>
<td>Metric IV</td>
<td>81.40</td>
<td>Proportion of trials with MTD in target dose region (&gt;= 5% - 20%)</td>
</tr>
<tr>
<td>Metric V</td>
<td>13.70</td>
<td>Proportion of trials with MTD in over dose region (&gt;= 20%)</td>
</tr>
<tr>
<td>Metric VI</td>
<td>0.40</td>
<td>Proportion of trials with MTD in under dose region (&lt; 5%)</td>
</tr>
<tr>
<td>Stopped</td>
<td>4.50</td>
<td></td>
</tr>
</tbody>
</table>

## Average N: 148.45
## Average DLT: 18.20
Simulation output

Detailed diagnostic plots

Reasonable doses?
DLT probability by dose

How often is each dose investigated?
Prop. of patients per dose
Prob(dose is investigated)

Reasonable selections?
Prob(dose selected as MTD)

How many patients (per dose/overall)?
Avg. sample size per dose
Prob(N = nn); triangle: N>=nn

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Discussion

- Historically, dose finding in malaria has been limited
  - Desirable to administer doses as high as possible (efficacy, resistance)
  - Ethically questionable to treat with doses expected to be subtherapeutic

- Dose finding program tailored to estimate the upper limit for dosing

- Methodology for Bayesian phase 1 oncology trials translates naturally to our setting

- Necessary (though perhaps not sufficient) ingredients
  - Open-minded clinical team
  - Frequent discussions with study team – favor visualizations over statistical jargon
  - Hypothetical examples of dose-escalation recommendations
  - Of course...
    - Familiarity with Bayesian statistics
    - Effort/willingness to conduct fairly large-scale simulations to evaluate the design
References & acknowledgements

- **Selected references:**
  - Schmidli H, Gsteiger S, Roychoudhury S, O’Hagan A, Spiegelhalter DJ, Neuenschwander B. Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics 2014*

- **Acknowledgments:**
  - Novartis malaria clinical team
  - Simon Wandel and Sebastian Weber (Novartis oncology)
Thank you!

Questions?