A web application for conducting the continual reassessment method

Nolan A. Wages, PhD

Biostatistics Shared Resource
University of Virginia Cancer Center

March 3, 2017

Dose-finding Setting

Initial Safety Trials

- Discrete set of dose levels $d_1, \ldots, d_k$
- Objective is to recommend a dose for further testing for efficacy in Phase II
- The highest dose with an "acceptable" rate of **dose-limiting toxicity (DLT; yes/no)** is the **maximum tolerated dose (MTD)**
- Probability of DLT, $R(d_1) < R(d_2) < \cdots < R(d_k)$
- Ultimate goal is to locate the MTD, defined as the dose level with DLT rate closest to a pre-specified target DLT rate θ; i.e. (20%, 25%, 30%, etc.)

Continual Reassessment Method (CRM)

O'Quigley, Pepe, and Fisher (Biometrics, 1990)

- Sequentially updates statistical model to obtain estimates of DLT probabilities at each dose
- Allocates next patient cohort to the dose with estimated DLT rate closest to the target rate θ
- After n patients, MTD is defined as the recommended dose level for patient $n + 1$
- Abundance of articles in statistical literature on superior performance of CRM over 3+3[1]
- Despite poor operating characteristics, 3+3 used $>$ 90.0% of published phase I oncology trials[2]

[1] Iasonos A, O'Quigley J (2014). *JCO* **32**: 2505-11.

[2] Paoletti et al. (2015). *Ann Oncol* **26**: 1808–12.

Reasons For Infrequent Use of CRM[1]

1. "Black-box" mentality from reviewers/clinicians
   - Poor understanding of how it works
2. Sensitivity to choice of design specifications
   - Working dose-toxicity model
   - Prior distributions
3. Computationally burdensome
   - Requires regular interaction between clinical and statistical team

[1] Cheung YK. *Dose-finding by the continual reassessment method*; CRC Press: New York, 2011.

Recommended Bayesian CRM Specifications

Good Operating Characteristics

- [1]Functional form of dose-toxicity model

$$R(d_i) = \Pr(\text{DLT at dose } d_i) \approx \alpha_i^{\exp(a)}$$

- [2]Initial guesses of DLT probabilities (skeleton) α_i
  - Algorithm for generating skeletons with reasonable spacing between adjacent values; i.e. $\alpha_i = \{0.10, 0.20, 0.30, 0.40, 0.50\}$
- [3]Prior distribution on model parameter a
  - $\mathcal{N}(0, 1.34)$ yields good operating characteristics in many practical situations.

[1] Paoletti X, Kramar A (2009). *Stat Med* **28**: 3012–3028.

[2] Lee SM, Cheung YK (2009). *Clin Trials* **6**: 227–38.

[3] O'Quigley J, Shen LZ (1996). *Biometrics* **52**: 673–684.

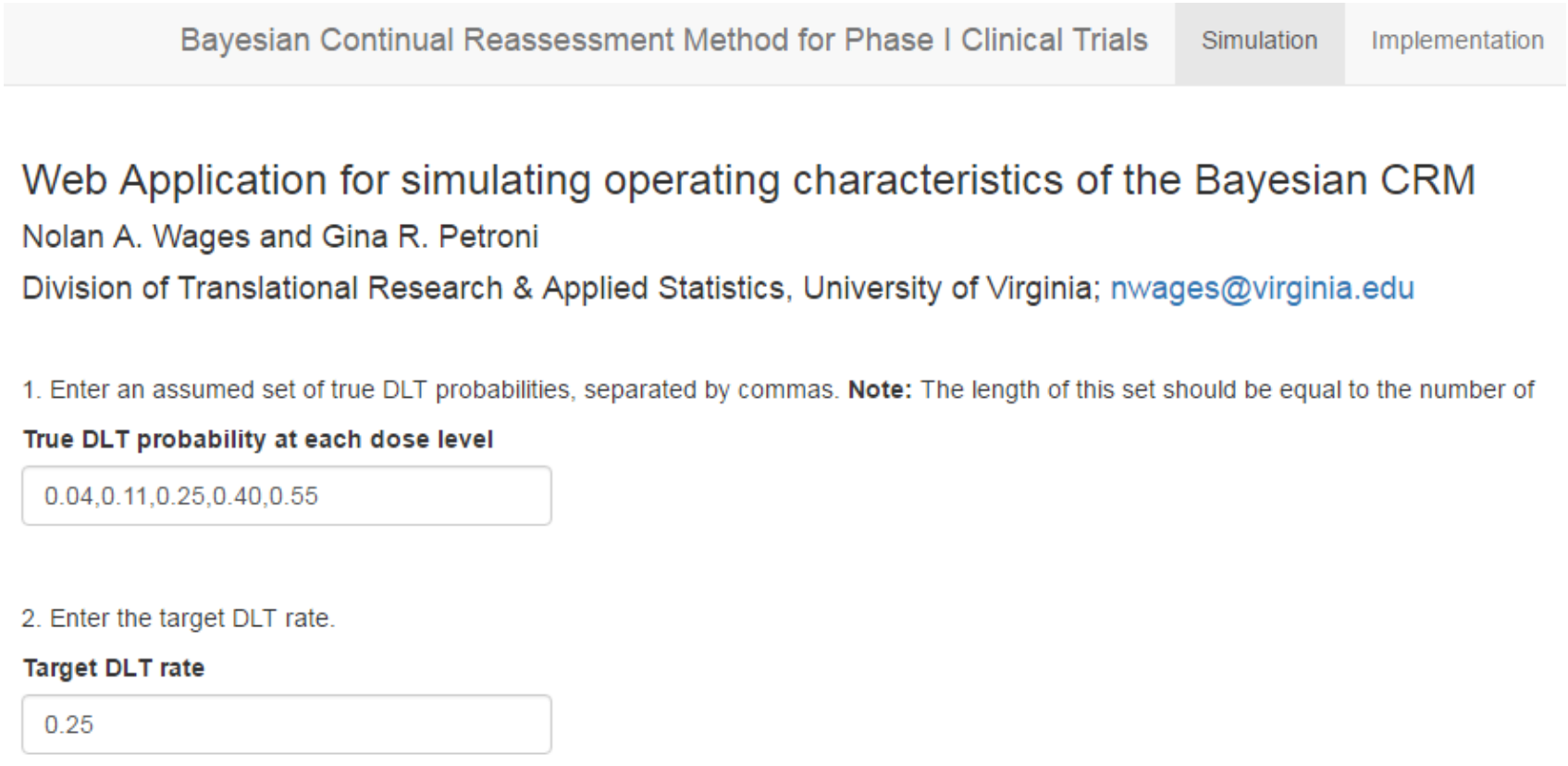
Motivation

Bayesian CRM Web Tool

- R packages requires some programming knowledge
- Current CRM software requires user to make a lot of design specification choices
  - Poor choices = poor design operating characteristics
- Lack of available software with default practical recommendations
- Goal: provide accessible software tools to be utilized at both the design stage and for direct protocol implementation with simple recommendations for design specifications.

Bayesian CRM Web Tool

https://uvatrapps.shinyapps.io/crmb/



Bayesian CRM Web Tool

https://uvatrapps.shinyapps.io/crmb/

- Simulates operating characteristics

Simulation	Implementation

- Computes the recommended dose level for the next patient based on accumulated data

Simulation	Implementation

Bayesian CRM Web Tool

Simulation Input 1–2

1. Enter an assumed set of true DLT probabilities, separated by commas.
   Note: The length of this set should be equal to the number of possible study dose levels

True DLT probability at each dose level

0.01, 0.05, 0.12, 0.25, 0.40

2. Enter the target DLT rate

Target DLT rate

0.25

Bayesian CRM Web Tool

Simulation Input 3–5

3. Enter the cohort size required before the next model-based update. Cohort size may be 1, 2, or 3 patients.

Cohort size

1

4. Enter the maximum sample size for the study. This number should be a multiple of the cohort size entered above.

Maximum number of patients

24

5. Enter the number of simulations. A minimum of 1000 is recommended.

Number of simulated trials

1000

Bayesian CRM Web Tool

Simulation Input 6–7

6. Enter the index of the starting dose level. **Note:** Index of lowest dose level is always 1. If the design allows for 'minus' dose levels (i.e. -2, -1, etc.), then the index of the starting dose should account for these lower levels (i.e. if -1 dose level allowed, starting dose is 2.)

Index of starting dose level

1

7. Set the seed of the random number generator.

Random seed

580

Run simulation study

Bayesian CRM Web Tool

Simulation Output

Skeleton of working model:	0.08	0.16	0.25	0.35	0.46
True DLT probability:	0.01	0.05	0.12	0.25	0.40
MTD selection percentage:	0.00	1.40	22.9	52.8	22.9
Average number of DLTs:	0.00	0.10	0.70	2.1	2.2
Average number of patients:	1.50	2.30	6.00	8.50	5.70
Accuracy index:	0.5353				
Percent stopped for safety:	0				

Accuracy Index

- For a sample size of n, accuracy index of Cheung (2011)

$$A_n = 1 - k \times \frac{\sum_{i=1}^{k} |R(d_i) - \theta| \Pr(\text{selecting dose } i)}{\sum_{i=1}^{k} |R(d_i) - \theta|},$$

  is a weighted average summary of the distribution of MTD recommendation.
- Its maximum value is 1 with larger values (close to 1) indicating that the method possesses high accuracy
- In the previous scenario, the value of A_n for an optimal benchmark (O'Quigley et al., 2002) was 0.6314.
  `https://uvatrapps.shinyapps.io/nonparbnch/`

[1] Cheung YK. *Dose-finding by the continual reassessment method*; CRC Press: New York, 2011.

Bayesian CRM Web Tool

Implementation Input 2–4

2. Enter number of observed DLTs at each dose level. If none have been observed or a dose level has not yet been tried, enter '0'. **Note:** The length of this set should be equal to the number of possible study dose levels.

Number of observed DLTs at each dose level

0, 0, 0, 0, 0

3. Enter the number of patients evaluated for DLT at each dose level. If a dose level has not yet been tried, enter '0'. **Note:** The length of this set should be equal to the number of possible study dose levels.

Number of patients evaluated for DLT at each dose level

1, 0, 0, 0, 0

4. Enter the most recent dose level administered in the study. Get updated recommended dose level.

Current dose level

1

Get updated recommended dose level

Bayesian CRM Web Tool

Implementation Output

Skeleton of working model:	0.08	0.16	0.25	0.35	0.46
Number of DLTs:	0	0	0	0	0
Number of patients:	1	0	0	0	0
Estimated DLT probabilities:	0.12	0.17	0.23	0.30	0.37
Target DLT rate:	0.25				
Recommended dose level:	2				

Bayesian CRM Web Tool

Updated Data

2. Enter number of observed DLTs at each dose level. If none have been observed or a dose level has not yet been tried, enter '0'. **Note:** The length of this set should be equal to the number of possible study dose levels.

Number of observed DLTs at each dose level

0, 0, 0, 0, 0

3. Enter the number of patients evaluated for DLT at each dose level. If a dose level has not yet been tried, enter '0'. **Note:** The length of this set should be equal to the number of possible study dose levels.

Number of patients evaluated for DLT at each dose level

1, 1, 0, 0, 0

4. Enter the most recent dose level administered in the study. Get updated recommended dose level.

Current dose level

2

Bayesian CRM Web Tool

Updated Output

Skeleton of working model:	0.08	0.16	0.25	0.35	0.46
Number of DLTs:	0	0	0	0	0
Number of patients:	1	1	0	0	0
Estimated DLT probabilities:	0.08	0.12	0.18	0.24	0.31
Target DLT rate:	0.25				
Recommended dose level:	3				

Notes

https://uvatrapps.shinyapps.io/crmb/

- Utilizes a set of default design specifications based on practical recommendations from literature
- These specifications produce robust operating characteristics.
  - Contains the type of simulation information that aid clinicians and reviewers in understanding operating characteristics for the accuracy and safety of the CRM
- The bottom of the web page contains detailed notes about the design specifications, including the skipping restriction and safety stopping rule.
  - For input in a protocol statistical section.

Conclusions

https://uvatrapps.shinyapps.io/crmb/

- The web tool provides a mechanism for conducting the Bayesian CRM in a timely and reproducible fashion, requiring no programming knowledge.
- Free to access and use on any device with an internet browser.
  - Can be used on a smart phone.
- We hope this leads to broader implementation of model-based designs and will facilitate more efficient collaborations within study teams.

Acknowledgements

- Funding:
  - NCI: K25181638
- Collaborators:
  - Gina Petroni, PhD
  - Mark Conaway, PhD
  - Beth Horton, PhD
  - John O'Quigley, PhD
  - Alexia Iasonos, PhD