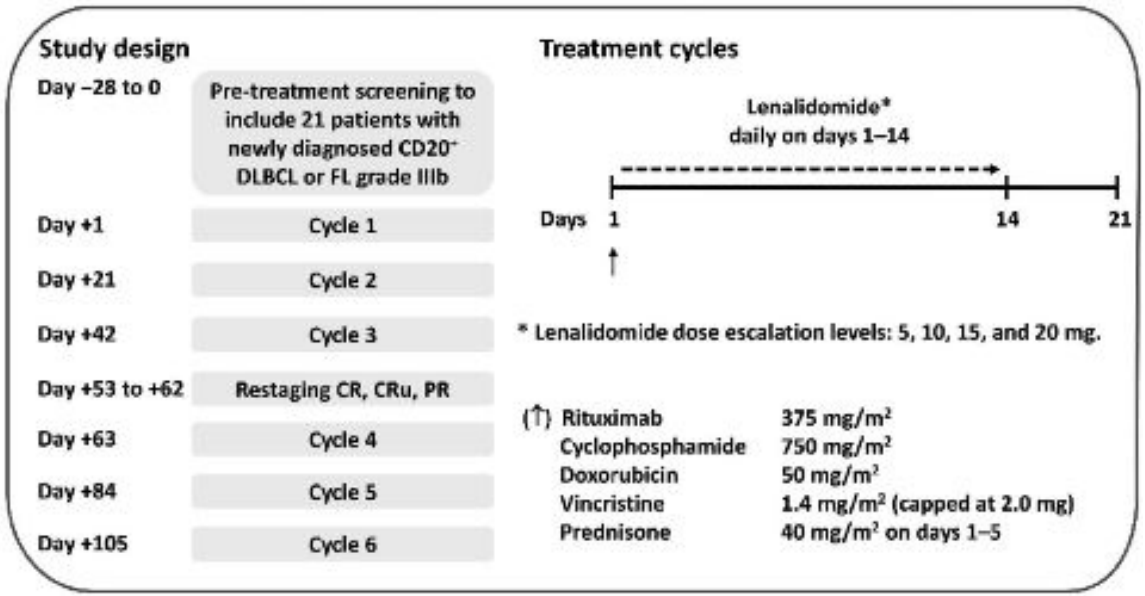
Bayesian Clinical Trials

Real data case study

Case Study (Chiappella et al, 2013)

- Primary endpoint: to determine the maximum tolerated dose (MTD) of lenalidomide given in combination with fixed doses of R-CHOP in elderly patients with untreated DLBCL.



Case Study (Chiappella et al, 2013)

- $d_{start} = 10$ mg/day
- DLT definition: the maximum dose inducing any grade ≥ 3 non-hematologic toxicity or a delay $>$15 days of a planned cycle date observed during the first two cycles
- TTL=33%
- dose levels: 5, *10*, 15, 20 mg/day
- CRM
- cohort size: 3

CRM

One parameter logistic model

$$P(Y = 1|x_i) = \psi(x_i, \theta) = \frac{\exp(a_0 + \theta x_i)}{1 + \exp(a_0 + \theta x_i)}$$

where

- Y_j is the binary variable indicating toxicity for the $j - th$ patient
- $x_i = \psi^{-1}(p_i, \theta)$ is the standardized dose level
- p_i the initial guesses of toxicity probability (i.e. $p_1 = 0.15,\ p_2 = 0.20,\ p_3 = 0.25$, and $p_4 = 0.30$
- a_0 is the intercept
- θ is to be estimated.

Steps

- choose a prior $\pi(\theta)$ for θ
- starting from d_{start}, compute sequentially, every after c patients (i.e. 3), the Bayesian posterior mean of the model parameter, $\tilde{\theta}_j$ as

$$E(\theta_j|data) = \int_0^\infty \theta f(\theta|data)\, d\theta$$

where $f(\theta|data)$ is the posterior density:

$$f(\theta|data) = \frac{L_j(\theta)\pi(\theta)}{\int_0^\infty L_j(u)\pi(u)\, du}$$

Steps

- compute $\psi\left(x_i, \tilde{\theta}_c\right)$ and the next 3 patients will be assigned to the (standardized) dose level, that minimizes the distance

$$|\psi\left(x_i, \tilde{\theta}_c\right) - TTL|$$

- after inclusion of m patients, the estimated probability of toxicity for the recommended dose level (at that point!), x_R, will be $\tilde{P}_{R|m} = \psi\left(x_R, \tilde{\theta}_m\right)$
- a 1-α credibility interval for $P_{R|m}$ is $(\theta_{min}; \theta_{max})$ where

$$\int_{\theta_{min}}^{\theta_{max}} f\left(\theta|data\right) d\theta = 1 - \alpha$$

- stop when the maximum sample size has been reached (i.e. n=24) or stopping rules have been fulfilled

Stopping rules (Zohar & Chevret, 2001)

Rules based on posterior distribution

$$w_1 = P\left[\psi\left(x_{first}, \tilde{\theta}\right) > TTL | data\right] \quad (1)$$

$$w_2 = P\left[\psi\left(x_{last}, \tilde{\theta}\right) < TTL | data\right] \quad (2)$$

$=>$ stop for wrong dose scale if $w_1 > 0.9$ or $w_2 > 0.9$

Stopping rules (Zohar & Chevret, 2001)

Rules based on predictive distribution of z future responses

$$w_3 = \tilde{P}(X(j+1) = \ldots X(j+z) \,|data) \tag{3}$$

$$w_4 = \sum_{y_1=0}^{1} \ldots \sum_{y_z=0}^{1} |\tilde{P}_{R|_{j+z}} - \tilde{P}_{R|_{j+1}}| P(Y_{j+1} = y_1, \ldots, Y_{j+z} = y_z | data) \tag{4}$$

$$w_5 = \max_{(y_1,\ldots,y_z)} |\tilde{P}_{R|_{j+z}} - \tilde{P}_{R|_{j+1}}| \tag{5}$$

$=>$ stop for futility if $w_3 > 0.9$

$=>$ stop for no mean predictive or no maximal predictive gain in point estimate of the estimated probability of toxicity if $w_4 < 0.05$ or $w_5 < 0.05$, respectively

Stopping rules (Zohar & Chevret, 2001)

$$w_6 = \sum_{y_1=0}^{1} \cdots \sum_{y_z=0}^{1} |c_{\alpha,j+z}(P_R) - c_{\alpha,j+1}(P_R)| P(Y_{j+1} = y_1, .., Y_{j+z} = y_z | data)$$

$$w_7 = \max_{(y_1,\ldots,y_z)} |c_{\alpha,j+z}(P_R) - c_{\alpha,j+1}(P_R)|$$

where $c_{\alpha,.}(P_R)$ is the width of the 100(1-α) credibility interval of the toxicity probability at the recommended dose level d_R.

$=>$ stop for no gain in accuracy of the estimated probability of toxicity if $w_6 < 0.05$ or $w_7 < 0.05$

Data

Cohort	Admin dose	Toxicity	5 mg	10 mg	15 mg	20 mg
1	10	(0,0,0)				
2	20	(1,1,0)				
3	15	(0,0,1)				
4	15	(1,0,0)				
5	15	(1,1,0)				
6	10	(0,0,1)				
7	10	(0,0,0)				

bcrm package

bcrm implements a Bayesian CRM (O'Quigley et al, 1990) and can run interactively, allowing the user to enter outcomes after each cohort has been recruited.

```
library(bcrm)
```

- Binary toxicity outcome
- Dose-toxicity models: Hyperbolic Tangent, Logistic (1-and 2-parameter) and Power
- Priors: Gamma, Uniform, Lognormal and Bivariate Lognormal
- Stopping rules: maximum sample size, minimum sample size in conjuction with precision of the MTD or maximum number treated ad MTD

R code

```
dose = c(5, 10, 15, 20)
p.tox0 = c(0.15, 0.20, 0.25, 0.3)
data = data.frame(patient=1:3, dose=rep(2,3), tox=rep(0,3))
target.tox = 0.33
bcrm(stop = list(nmax=24, precision=c(0.16,0.6)),
     data = data,
     p.tox0 = p.tox0,
     dose = dose,
     ff = "logit1",
     prior.alpha = list(3, a=1, b=0.75),
     target.tox = target.tox,
     sdose.calculate = "mean",
     constrain = FALSE
     )
```

References

- Chiappella A, Tucci A, Castellino A et al. Lenalidomide plus cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab is safe and effective in untreated, elderly patients with diffuse large B-cell lymphoma: a phase I study by the Fondazione Italiana Linfomi. Haematologica 2013; 98(11): 1732-1738.
- Zohar S, Chevret S. The continual reassessment method: comparison of Bayesian stopping rules for dose-ranging studies. Stat Med 2001; 20: 2827-2843.
- O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase I clinical trials in cancer. Biometrics 1990; 46: 33-48.