Blinded Bayesian Adverse Event Monitoring

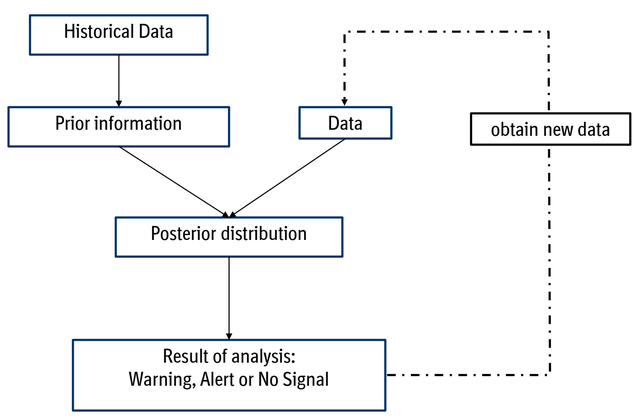
Oliver Sailer*, Timo Bailer

Boehringer Ingelheim Pharma GmbH & Co. KG, 88397 Biberach an der Riss, Germany

* martin_oliver.sailer@boehringer-ingelheim.com

Background

- Blinded AE monitoring during conduct of Biosimilar trial
- Historical information about AE terms of interest from originator
- Put AE on trial in context with historical data
  - AE rate unexpectedly low/high?
  - Further investigation required?



Prior information

- Probability p that patient experiences AE
- Originator trial with N_H patients, $N_H\widehat{p_H}$ experienced event
- Weight γ for prior information

$$p \sim Beta(\gamma N_H \widehat{p_H}, \gamma N_H (1-\widehat{p_H}))$$

- Choose weight s.t. prior is informative especially early on but trial data not dominated
- Could consider formal meta-analysis on historical trials for p and resulting prior effective sample size [1]

Data updating

- Observed data X_i (at time point t_i)
- Indicator for patient j with AE: $Y_{j,i}$
  - $Y_{j,i}$ = 0: The patient never experienced this AE
  - $Y_{j,i}$ = 1: The patient experienced this AE at least once
- Assume same probability p for each of N_i patients
- Binomial likelihood for $Y_i = \sum_j Y_{j,i}$

$$Y_i | p \sim Bin(N_i, p)$$

X_1 at timepoint t_1	
Patient ID	y_{AE}
#001	0
#002	1
...	...
#100	0

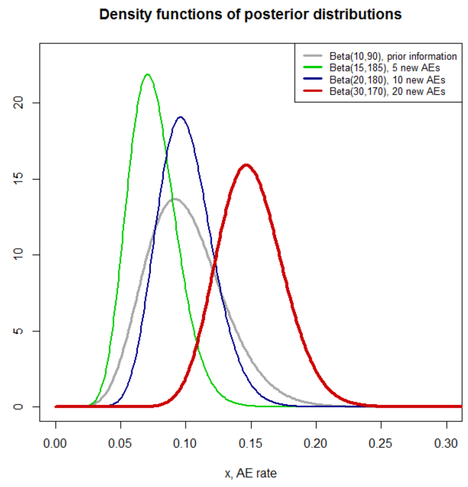
X_2 at timepoint t_2	
Patient ID	y_{AE}
#001	1
#002	1
...	...
#100	0
#101	1
...	...
#200	0

X_3 at timepoint t_3	
Patient ID	y_{AE}
#001	1
#002	1
...	...
#100	0
#101	1
...	...
#200	0
#201	0
...	...
#300	1

Posterior distribution

- Conjugate Beta distribution [2]
- Posterior is Beta as well

$$p | Y_i = y_i \sim Beta(\gamma N_H \widehat{p_H} + y_i, \gamma N_H (1-\widehat{p_H}) + N_i - y_i)$$

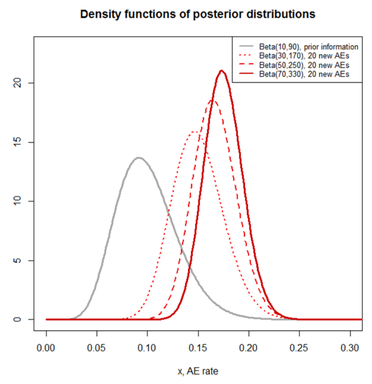


Monitoring

- If AE rate throughout ongoing trial higher than expected from historical data, posterior will describe increasingly higher AE rate converging to new AE rate

Example:

- At every time point 100 additional patients
- At every time point, 20 additional patients with AE
- t0 : effective data 100 patients, 10 with AE
- t1 : historical data + data X1 (100 patients, 20 with AE)
- t2 : historical data + data X2 (200 patients, 40 with AE)
- t3 : historical data + data X3 (300 patients, 60 with AE)



Decision criteria

- Warning or Alert if posterior AE rate greater than a predefined threshold with a certain trigger probability
- Warning

$$P(p|Y_i > \delta_W) > \alpha_W$$

- Alert

$$P(p|Y_i > \delta_A) > \alpha_A$$

- Otherwise consider "safe"
- Thresholds and trigger probabilities tbd with medical input
- Trade-off between too many false alarms and risk of overlooking signal

Choice of parameters

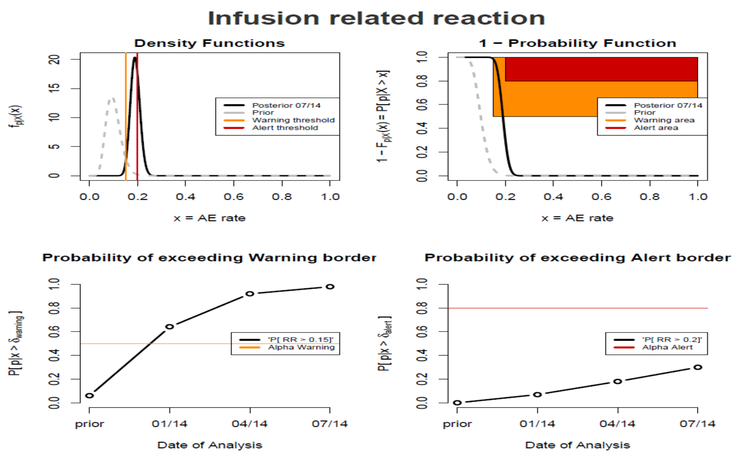
- Simulation example [3]
- Historical data with $\widehat{p_H}$, weighted size
- m monitoring time points in new phase III trial
- Assume medical input was: safe if "true" RR in new trial is 1, warning if RR is 2, alert if RR is 3
- α_W=0.5, α_A=0.8
- Probabilities to decide on Alert (A), Warning (W) or Safe (S) at k-th monitoring

Scenario	Analysis k		
	A	W	S
RR_3	$p^k_{3,A}$	$p^k_{3,W}$	$p^k_{3,S}$
RR_2	$p^k_{2,A}$	$p^k_{2,W}$	$p^k_{2,S}$
RR_1	$p^k_{1,A}$	$p^k_{1,W}$	$p^k_{1,S}$

- Select δ_W, δ_A to minimize probabilities for incorrect decision
- Can flexibly put emphasis
  - high probability of issuing alert if RR=3 at last monitoring
  - high probability to not issue an alert at last monitoring if RR=1
  - Mistakenly issuing a warning is less critical than mistakenly issuing an alert

Output

- Historical data with $\widehat{p_H}$ =0.1, γN_H=100
- Analysis every 3 months 100 new observations
- Risk Ratio = 2
- Warning δ_W=0.15, α_W=0.5
- Alert δ_A=0.20, α_A=0.8



Summary table

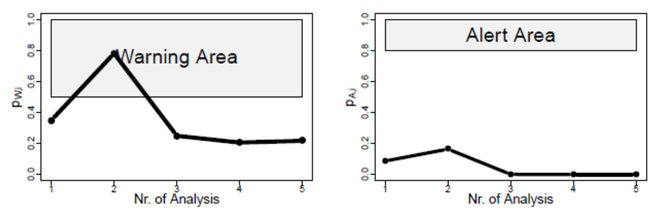
Date	AEs	N	P[RR > 1.5]	P [RR > 2]	E[$p\|Y_i$]	Std. dev.	95 % Credible Interval	Signal
Prior	10	100	6 %	0 %	0.10	0.03	[0.05 , 0.17]	None
01/14	30	200	48 %	3 %	0.15	0.03	[0.10 , 0.20]	None
04/14	50	300	78 %	7 %	0.17	0.02	[0.13 , 0.21]	Warning
07/14	70	400	91 %	10 %	0.18	0.02	[0.14 , 0.21]	Warning

Retrospective application

- Lung cancer, historical data:
  - patients with diarrhoea of CTC grade ≥3
  - $\gamma N_H = 50, \widehat{p_H}$=0.03
- Warning δ_W=0.04, α_W=0.5
- Alert δ_A=0.068, α_A=0.8
- Re-sampled data from a lung cancer trial [4]
- Interim monitoring every 3 months

- Between 1st and 2nd analysis 8 new events on only 129 patients
- 2nd analysis: posterior mean of 0.06

i	y_i	$N_i - y_i$	N_i
1	1	19	20
2	9	140	149
3	15	410	425
4	24	662	686
5	28	760	788



- Comparison of 95% credible interval from posterior distribution and 95% Wilson score confidence interval

AE	i	Credible Interval		Confidence Interval	
		L_i	U_i	$\tilde{L}_i$	$\tilde{U}_i$
Diarrhoea (Grade≥ 3)	1	0.61	8.97	0.89	23.61
	2	2.63	8.77	3.21	11.08
	3	2.02	5.3	2.15	5.74
	4	2.27	4.9	2.36	5.15
	5	2.38	4.87	2.47	5.09

Discussion

Easy to motivate to medical/drug safety

Applicability

- Can use for single arm trials in general
- Consider pooled blinded analysis for superiority trial to combine historical information on comparator and earlier phase information on new drug
- (Partially) unblinded analyses for IDMC

AE probability depends on time at risk/exposure

- AE rate at end of trial overestimates AE rate while trial ongoing
- Time at risk not considered/not controlled between trials
- Simple proportions of patients with an AE the appropriate measurement?
- Time-to-event information on AE available on own substance from earlier development phases but not on comparator
- AE rate at end of comparator trial overestimates AE rate while trial ongoing unless AE occurs early if it occurs at all

References

[1] Neuenschwander, B et al. (2010). Summarizing historical information on controls in clinical trials. *Clinical Trials* **7**, 5–18.

[2] Berry, SM et al. (2010). *Bayesian adaptive methods for clinical trials*. CRC press.

[3] Bailer, T (2014): Bayesian Decision Criteria in Clinical Development. Master's thesis, Ulm University.

[4] Reck, M et al. (2014). Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. *The lancet oncology* **15**, 143–155.

6th Bayes Pharma Conference

19-22 May 2015, Basel Switzerland

BAYES2015 BASEL