

# A Forward-looking Covariate-adjusted Response-adaptive Patient Randomisation Rule:

Delivering Personalised Treatments, Patient Benefit  
and Power Gains in Multi-armed Trials

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**This talk is based on joint work with Prof. W. Rosenberger (GMU)**

# Outline

Motivation & Background: The Challenge of Personalised Medicine

A Novel Approach: CARA Forward-looking Gittins Index

Some Simulations Results

Discussion

# Tailoring Treatment to a Patient's Characteristics

## Testing Several Arms in Few Patients

- FDA approved several cancer drugs for use in patients whose tumours have specific genetic characteristics (identified by a diagnostic test). Also, for cystic fibrosis patients with a specific genetic mutation.
- This has strengthened the promise of “*personalised medicine*” - the tailoring of treatment to the individual characteristics of each patient.
- The challenge is **how** can we answer which patients respond differently to a treatment in contexts in which there are **several promising new treatments** and **relatively few patients** to test them - even fewer patients if a treatment works only within a subgroup.
- Research for personalised medicine requires **methodology** for trial design to **identify superior treatments** among several arms more **quickly**, mainly treatments that work better **within subgroups**.

# Response-adaptive Randomisation and Covariates

Assigning More Patients to Better Treatment based on their Profile

- Response-adaptive randomisation (RAR) alters the allocation probabilities based on **observed outcomes** up to that patient.

The usual goal is to achieve some *ethical* or *statistical objective*.

- Covariate-adjusted Response-adaptive (CARA) alters the allocation probabilities given **observed outcomes** and covariates and the current patient's covariate profile.

CARA designs can benefit patients (in case of a treatment-covariate interaction) by skewing the allocation probabilities to the better performing treatment among patients with a similar covariate profile.

- ! Note that CARA early covariate-adaptive methods (1970s) try to induce **balance** between treatment groups with respect to covariate margins: Pocock and Simon (1975); Taves, D. R. (1974); Wei, L.J. (1978). Balance does not lead to **efficiency** or **ethically attractive** designs (Rosenberger and Sverdlov, 2008).

# Limitations of Existing CARA Procedures

## Developing Efficient Non-myopic Randomised CARA Procedures

- (1) Almost all RAR procedures are **myopic** - be they Bayesian or not - adapt based on past data only and not potential future data.

Forward looking RAR procedures are **computationally expensive** and **deterministic**. Recent work proposed a randomised tractable non-myopic RAR algorithm using *bandit* theory. Villar et al (2015)

- (2) RAR procedures with ethical goals have considerably higher variability (**low power**) and other estimation issues (Villar et al , 2015).

E.g. CARA procedure Rosenberger, Vidyashankar and Agarwal (2001)

- In Villar and Rosenberger (2018) we develop a non-myopic CARA procedure with **patient benefit advantages** which is:

**computationally feasible** (implementable);  
**randomised** (selection bias control);  
**efficient** in the multi-armed case (high power);

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# The Multi-armed Bandit Problem and the Gittins Index

## Introducing Randomization to Bandit Strategies

- The multi-armed bandit problem (MABP): optimal allocation of treatments to patients with an **overall patient benefit** goal.
- The Gittins Index (GI) (Gittins and Jones, 1979) is a **tractable** rule that recovers the (intractable) optimal solution to the MABP.

**Both the MABP and the GI use a Bayesian updating procedure.**

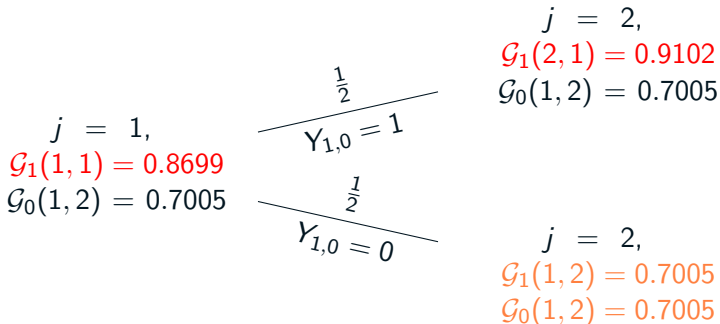
- Despite its tractability and considerable ethical advantages a main barrier to its use is the **lack of randomisation** of treatment allocations.
- Villar et al (2015) defined a block randomised procedure based on the GI. FLGI allocation probabilities:  $\pi_{k,j}$ , the probability of allocation to treatment  $k$  at stage  $j$  - common to all patients in block  $j$ - when using the GI and given observed responses up to block  $j-1$ .

# The Forward Looking Gittins Index

## Introducing Randomization to the Gittins Index Rule

Assume that  $T$  patients arrive sequentially in blocks of size  $b$  over  $J$  stages, so that  $J \times b = T$ . In Villar et al (2015) we defined **group allocation probabilities** based on the Gittins Index (GI) rule as follows:

Simplest example:  $b = 2$ . Priors: control  $(s_{(0,0)}, f_{(0,0)}) = (1, 2)$  and experimental  $(s_{(1,0)}, f_{(1,0)}) = (1, 1)$



What is the (patient-average) probability of each arm being allocated in the next block using the GI (and given the priors)?

$$\pi_{1,0} = \frac{(0 \times 1) + (0 \times 1/2 + 1/2 \times 1/2)}{2} = 1/8, \pi_{1,1} = \frac{(1 \times 1) + (1 \times 1/2 + 1/2 \times 1/2)}{2} = 7/8.$$

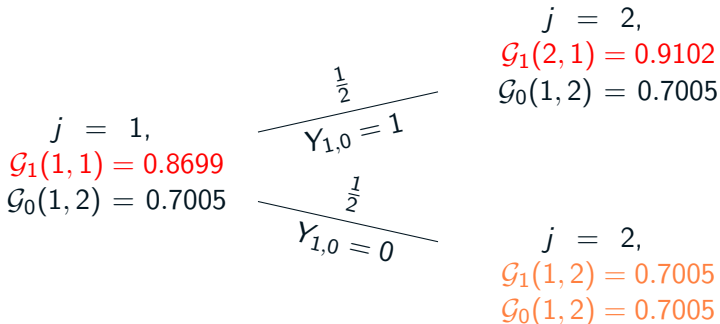


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# FLGI Probabilities: Computation & Properties

## A Non-myopic Group Randomised Procedure

- C Just as for the MABP, the computational cost of the exact FLGI probabilities grows with the number of arms ( $K$ ) and  $b$  (block size).

Computation in practice can be done via Monte Carlo simulation.

Example:  $\mathbf{P} = [1 \ 1 ; 2 \ 1 ; 1 \ 2 ; 2 \ 2]$  ( $K = 4$ ) and block  $b = 9$  then  $\pi \approx [0.2646 ; 0.5901 ; 0.0246 ; 0.1208]$  after  $5 * 10^2$  replicas.

- P1 For **equal priors** the algorithm defines **equal allocation probabilities**.
- P2 As the block size tends to grow (in the limit it equals the trial size), the design tends to a **balanced design** (given initial equipoise).
- P3 If the block is of only 1 patient (i.e. there is an interim after every patient), the FLGI rule recovers the **GI rule**.

# Introducing Covariates to the Gittins Index Rule

## Deriving a CARA FLGI Rule

- (1) We consider a MABP with  $K$  experimental arms, a control arm and  $T$  patients. Before arm  $k$  is allocated to patient  $t$ , a **binary covariate**  $Z_t$  is observed. Immediately after, a binary response  $Y_{t,n}$  is observed.
- (2) Reformulate the above MABP: for every treatment-covariate combination there exists a **combination arm**  $kz$ . E.g., the arm “00” corresponds to the control arm and covariate negative patients.

New **reformulated** MABP has  $2(K + 1)$  combinations arms (with rate  $p_{kt}$ ) and patients are optimally allocated to arms with the constraint that they are only allowed arms feasible given their biomarker profile.

- (3) We defined a **modified** GI rule: each patient gets the treatment with the highest GI among the arms **available for their biomarker profile**.
- (4) From this modified GI, a randomised group allocation procedure is defined as in Villar et al (2015) but for every covariate value (and block) we have a different vector of allocation probabilities  $\pi_{k,j}(Z)$ .

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# The CARA FLGI in Practice

## Simulation Results

3-arm trial 300 patients  $p_{k0} = (0.22; 0.34; \mathbf{0.49})$ ,  $p_{k,1} = (0.47; \mathbf{0.71}; 0.37)$ .

Treatment-covariate interaction: **best** arm for covariate **negative** patients is **arm 2** while for covariate **positive** patients is **arm 1**.

	Power		Patient Benefit		
	$(1 - \beta_0)$	$(1 - \beta_1)$	$p_0^*$ (s.d)	$p_1^*$ (s.d)	ENS (s.d)
ER ( $b=300$ )	0.77	0.69	0.33 (0.04)	0.33 (0.04)	<b>132.01 (8.4)</b>
Thompson ( $b=10$ )	0.71	0.75	0.49 (0.09)	0.59 (0.09)	149.28 (9.5)
CARA C FLGI ( $b=10$ )	<b>0.82</b>	<b>0.88</b>	<b>0.52 (0.13)</b>	<b>0.64 (0.05)</b>	<b>151.44 (9.4)</b>
CARA FLGI ( $b=10$ )	0.24	0.06	0.78 (0.18)	0.89 (0.13)	171.25 (11.2)
CARA GI ( $b=1$ )	0.08	0.04	0.70 (0.29)	0.94 (0.06)	<b>171.42 (11.5)</b>

CARA FLGI probabilities (Monte Carlo simulation),  $T = 300$ ,  $p_z = 0.5$  and 5000 runs.

- **Treatment-covariate interactions are detected** by the CARA (Covariate-Adjusted Response Adaptive) FLGI procedure but its statistical power is very low.
- In a multi-armed case the CARA CFLGI addresses the power limitation (though in a two-arm setting power may be insufficient).

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# Discussion & Extensions

## Trials for Personalised Treatment & Including Patient Benefit Goals

- Derivation of the CARA FLGI probabilities is considerably more complex than competing methods yet its implementation is as feasible as other methods.
- Non-myopic methods offer increased patient benefit (quickly identify best arm) yet have lower power. Power may be improved in a two-armed context at the expense of patient benefit gains.
- Multi-armed trials simulations: patient benefit increases with the number of arms and a protected method achieves both power-ethical advantages (“protecting allocation to control arm” - CARA CFLGI).
- Extensions: **polychotomous** (every treatment-covariate combination as an arm) and **multiple** covariates (redefine all the covariates into a single covariate with multiple stratification levels as an arm).
- Fully Bayesian CARA FLGI: larger patient benefit/efficiency gains if historical data is combined with the RAR through the initial prior.

# References I

## Questions & Comments

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## Questions & Comments

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