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REDCap™

Extending REDCap Randomisation Beyond the Stratified List

Luke Stevens 16-Sep-2019

https://doi.org/10.25374/MCRI.9784550

Summary

Extending REDCap's Randomisation Capabilities to facilitate

Bayesian Adaptive Randomisation

and dynamic randomisation via

Biased Coin Minimisation

for the FORMAT Trial.

The Stratified List

- Randomise to avoid bias.
- Aim to balance the number of participants allocated to each allocation group,
  e.g. intervention vs. control.
- Randomisation to allocation group is not random!
- Allocate sequentially from a list generated in advance.
- Blocks of varying size and permutation.

Block	Entry	Group
1	1	I
1	2	C
1	3	C
1	4	I
2	1	I
2	2	C
3	1	C
3	2	I
…		

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1	1	I	
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1	3	C	
1	4	I	
2	1	I	
2	2	C	
3	1	C	
3	2	I	
…			

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Block	Entry	Group	Used
1	1	I	🚹
1	2	C	🚹
1	3	C	
1	4	I	
2	1	I	
2	2	C	
3	1	C	
3	2	I	
…			

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2	2	C	
3	1	C	
3	2	I	
…			

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  e.g. intervention vs. control.
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- Allocate sequentially from a list generated in advance.
- Blocks of varying size and permutation.
- Strata to balance within sub-populations.

Stratum: M				Stratum: F			
Block	Entry	Group	Used	Block	Entry	Group	Used
1	1	I	🚹	1	1	C	🚺
1	2	C	🚹	1	2	I	🚺
1	3	C	🚹	2	1	I	
1	4	I		2	2	C	
2	1	I		2	3	I	
2	2	C		2	4	C	
3	1	C		3	1	C	
3	2	I		3	2	I	
…				…			

The Stratified List: Limitations

Traditional Randomised Controlled Trial design has a long and successful history, but:

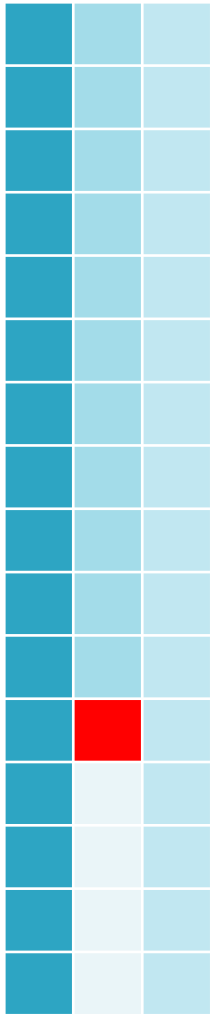
- Trial design and statistical analysis laid down in advance.
- Trade off predictability (small blocks) with imbalance from incompletely allocated (larger) blocks.
- Cannot weight stratification factors.
- No capacity to vary allocations or allocation ratios while trial in progress.
- "One population, one drug, one disease"
  → high costs, slow progress, high failure rate.

Beyond the Stratified List: Adaptive Designs

FDA: Adaptive design

"allows for prospectively planned modifications … based on accumulating data from subjects"

- Many different types, but potential modifications must be pre-specified.
- Example: response-adaptive randomisation:
  - More participants get promising treatments, ineffective treatments discarded.
- Can be more efficient when there is uncertainty around treatment effects (e.g. effectiveness, toxicity).



Beyond the Stratified List: Adaptive Designs

- "Basket"
  > evaluating multiple treatments for a single condition.

- "Umbrella"
  > evaluating one treatment (drug) for multiple conditions.

- "Platform":
  - Basket + Umbrella: multiple treatments, multiple conditions/populations.

FORMAT

Finding the Optimal Regimen for Mycobacterium Abscessus Treatment

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"Treatment regimens for Mycobacterium abcessus (MABS) are highly variable, not evidence-based and involve complex, expensive and often poorly tolerated drug combinations for prolonged periods."

Aims:

- To build an iterative, standing, platform trial with innovative and adaptive properties to evaluate combinations of therapies for patients with MABS-PD (MABS pulmonary disease).
- Test therapies that are currently used and recommended in published international consensus guidelines and are the basis for the current treatment guidelines for MABS-PD.
- Once the best combinations have been established the platform described in the Master Protocol will have the capacity to add new treatments and to eliminate therapies because of futility as they either lack efficacy or cause unacceptable toxicity.
- The data obtained as part of the trial will be used to plan for new waves of the platform trial using novel therapeutic approaches that may be tested against the previously determined optimal approaches, thus leading in an iterative fashion to improving microbiological clearance and health outcomes associated with MABS-PD.

FORMAT

Finding the Optimal Regimen for Mycobacterium Abscessus Treatment

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Why a platform – adaptive – approach for the FORMAT trial?

- MABS patient populations are very heterogeneous.
- Wide variety of treatment options in common usage.
- No strong evidence around relative effectiveness of common treatment regimens.

- Not possible to conceive a practical traditional trial design with reliable assumptions.
- Only the adaptive approach can facilitate

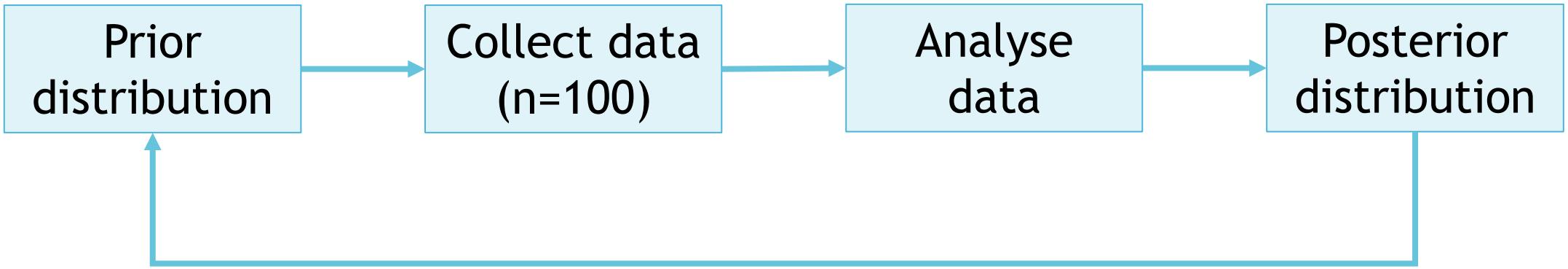
"Finding the Optimal Regimen"…

How to implement a platform approach for the FORMAT trial?

- Bayesian Adaptive Randomisation (BAR):
  - Define interim rules for dropping or adding treatment arms.
- Biased Coin Minimisation (BCM):
  - Stratified list is not an option because
    > treatments arms will change
    > stratification factors weighted differently
  - Adaptive randomisation algorithm required.

Bayesian Adaptive Randomisation (BAR)

- Iterative process.
- Interim analysis results utilised to define parameters for next iteration.



- Pre-specified changes only.

Adaptive Randomisation: Biased Coin Minimisation

Three step process:

1. Compute an imbalance score for each treatment based on previous allocations and target allocation ratio.

2. Select the treatment with the smallest imbalance score as "preferred".

3. Calculate allocation probabilities according to preferred treatment and ratio.

Randomization by minimization for unbalanced treatment allocation - Han - 2009 - Statistics in Medicine - Wiley Online Library

REDCap External Module

- Three randomisation events.
  - Different stratification factors.
  - Different factor weightings.
- Bayesian Adaptive Randomisation
  - Dynamically configurable mid-trial.
- Biased Coin Minimisation
  - Necessary to support adaptivity.
  - Scope for weighting factors differently.

Randomization

Setup | Dashboard | Simulate

Set JSON configuration in External Module project settings. Configuration is currently set to:

```
[
    {
        "allocation_field": "r1_grp",
        "allocation_event": "day_0_arm_1",
        "randomiser": {
            "class": "BiasedCoinMinimisation",
            "config": {
                "factors_weights": [
                    { "factor_name": "r1_resist", "weighting": 0.5 },
                    { "factor_name": "r1_agecat", "weighting": 0.2 },
                    { "factor_name": "r1_sex", "weighting": 0.1 },
                    { "factor_name": "r1_loc", "weighting": 0.1 },
                    { "factor_name": "r1_cf", "weighting": 0.1 }
                ],
                "allocations_ratios": [
                    { "group": "1", "ratio": 1 },
                    { "group": "2", "ratio": 1 },
                    { "group": "3", "ratio": 1 }
                ],
                "base_assignment_probability": 70
            }
        }
    },
    {
        "allocation_field": "r2_mabsposgrp",
        "allocation_event": "week_6_arm_1",
```

REDCap External Module

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Randomisation1

Data Access Group: **1101 AUS Site 01**

Editing existing Record ID **10151-1**

Event Name: **Day 0**

Record ID	10151-1
Age at randomisation (years)	4 View equation
Macrolide resistance * must provide value	Yes
Age category * must provide value	Less than 12 years
Sex * must provide value	Female
Location * must provide value	AUS/NZL
Cystic fibrosis * must provide value	Yes
Randomisation 1 Stratification	
Randomisation 1 date/time * must provide value	18-09-2019 06:28:05 Now D-M-Y H:M:S
Randomisation 1 Group Allocation	
Randomised allocation 1	Randomise
Form Status	

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Randomisation 1 Group Allocation	
Randomised allocation 1	Intensive A
Form Status	

REDCap External Module

- Comprehensive logging of allocation steps and calculations.
- API method for validation simulations.

randDBtest.R*

Source on Save | Run

```r
#no: of simulations and randomizations
nsims=500 #no: of simulations/runs
nrand=100 #no: of randomizations within a simulation
t1<-proc.time()[[3]]

simRecords=list()

#for each simulation run
for (i in 1:nsims){

  #1.clear the database: reset the target project (i.e. delete all records and reset
  y<-postForm(uri=api_url_reset,
              token = secret_token,
              curl = curl_handle)


  set.seed(20190625+i)
  site=paste0("s",sample(1:10,nrand,replace = T))
  sex=as.character(sample(1:2,nrand,replace = T))
  #NOTE: sex and site should be replaced by the actual minimisation factors

  result=list()
```

		(Day 0)	
18/09/2019 06:33	luke.stevens	External Module extended_randomisation_v0.0.2 Record 10151-1 (Day 0)	-Imbalance score for Factor r1_agecat=1 (weighting 0.2), Group=2 = 2/(2+0.1) = 1, weighted = 1 x 0.2 = 0.2
18/09/2019 06:33	luke.stevens	External Module extended_randomisation_v0.0.2 Record 10151-1 (Day 0)	-Factor r1_agecat=1 Group counts: 1 current=0, adjusted=(0+0)/1=0; 2 current=0, adjusted=(0+1)/1=1; 3 current=0, adjusted=(0+0)/1=0;
18/09/2019 06:33	luke.stevens	External Module extended_randomisation_v0.0.2 Record 10151-1 (Day 0)	-Imbalance score for Factor r1_resist=1 (weighting 0.5), Group=2 = 2/(2+0.1) = 1, weighted = 1 x 0.5 = 0.5
18/09/2019 06:33	luke.stevens	External Module extended_randomisation_v0.0.2 Record 10151-1 (Day 0)	-Factor r1_resist=1 Group counts: 1 current=0, adjusted=(0+0)/1=0; 2 current=0, adjusted=(0+1)/1=1; 3 current=0, adjusted=(0+0)/1=0;
18/09/2019 06:33	luke.stevens	External Module extended_randomisation_v0.0.2 Record 10151-1 (Day 0)	Total marginal imbalance score for Group=1 = 0.5+0.2+0.1+0.1 = 1
18/09/2019 06:33	luke.stevens	External Module extended_randomisation_v0.0.2 Record 10151-1 (Day 0)	-Imbalance score for Factor r1_cf=1 (weighting 0.1), Group=1 = 2/(2+0.1) = 1, weighted = 1 x 0.1 = 0.1
18/09/2019 06:33	luke.stevens	External Module extended_randomisation_v0.0.2 Record 10151-1 (Day 0)	-Factor r1_cf=1 Group counts: 1 current=0, adjusted=(0+1)/1=1; 2 current=0, adjusted=(0+0)/1=0; 3 current=0, adjusted=(0+0)/1=0;
18/09/2019 06:33	luke.stevens	External Module extended_randomisation_v0.0.2 Record 10151-1 (Day 0)	-Imbalance score for Factor r1_loc=1 (weighting 0.1), Group=1 = 2/(2+0.1) = 1, weighted = 1 x 0.1 = 0.1
18/09/2019 06:33	luke.stevens	External Module extended_randomisation_v0.0.2 Record 10151-1 (Day 0)	-Factor r1_loc=1 Group counts: 1 current=0, adjusted=(0+1)/1=1; 2 current=0, adjusted=(0+0)/1=0; 3 current=0, adjusted=(0+0)/1=0;
18/09/2019 06:33	luke.stevens	External Module extended_randomisation_v0.0.2 Record 10151-1 (Day 0)	-Imbalance score for Factor r1_sex=2 (weighting 0.1), Group=1 = 2/(2+0.1) = 1, weighted = 1 x 0.1 = 0.1
18/09/2019 06:33	luke.stevens	External Module extended_randomisation_v0.0.2 Record 10151-1 (Day 0)	-Factor r1_sex=2 Group counts: 1 current=0, adjusted=(0+1)/1=1; 2 current=0, adjusted=(0+0)/1=0; 3 current=0, adjusted=(0+0)/1=0;
18/09/2019 06:33	luke.stevens	External Module extended_randomisation_v0.0.2 Record 10151-1 (Day 0)	-Imbalance score for Factor r1_agecat=1 (weighting 0.2), Group=1 = 2/(2+0.1) = 1, weighted = 1 x 0.2 = 0.2
18/09/2019 06:33	luke.stevens	External Module extended_randomisation_v0.0.2 Record 10151-1 (Day 0)	-Factor r1_agecat=1 Group counts: 1 current=0, adjusted=(0+1)/1=1; 2 current=0, adjusted=(0+0)/1=0; 3 current=0, adjusted=(0+0)/1=0;
18/09/2019 06:33	luke.stevens	External Module extended_randomisation_v0.0.2 Record 10151-1 (Day 0)	-Imbalance score for Factor r1_resist=1 (weighting 0.5), Group=1 = 2/(2+0.1) = 1, weighted = 1 x 0.5 = 0.5
18/09/2019 06:33	luke.stevens	External Module extended_randomisation_v0.0.2 Record 10151-1 (Day 0)	-Factor r1_resist=1 Group counts: 1 current=0, adjusted=(0+1)/1=1; 2 current=0, adjusted=(0+0)/1=0; 3 current=0, adjusted=(0+0)/1=0;
18/09/2019 06:33	luke.stevens	External Module extended_randomisation_v0.0.2 Record 10151-1 (Day 0)	Stratification values are r1_resist=1 r1_agecat=1 r1_sex=2 r1_loc=1 r1_cf=1
18/09/2019 06:33	luke.stevens	External Module extended_randomisation_v0.0.2 Record 10151-1 (Day 0)	***** Biased Coin Minimisation: Record 10151-1 *****

Summing Up

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- FORMAT First Patient First Visit scheduled for October 2019.
- Demand for adaptive designs is increasing.
- Developing expertise in adaptive trials is a strategic focus for us.

- Opportunities for REDCap in this space? Innovation!
  - Better support for common double-blind randomisation (allocate a randomisation number, not a group) / code break?
  - Extend core functionality (or hook points, API method) to support more types of randomisation e.g. BCM algorithms?
  - Multiple randomisations per project?
  - Supporting adaptive trials (i.e. mid-trial alterations)?

Further Reading

- **The Platform Trial: An Efficient Strategy for Evaluating Multiple Treatments**
  Scott M Berry, Jason T Connor, Roger J Lewis
  JAMA; DOI 10.1001/jama.2015.2316
- **Twenty-five years of confirmatory adaptive designs: opportunities and pitfalls**
  Peter Bauer, Frank Bretz, Vladimir Dragalin, FranZ Konig and Gernot Wassmer
  Statistics in Medicine; DOI 10.102/sim.6472
- **Adaptive design clinical trials: review of the literature and ClinicalTrials.gov**
  Laura E Bothwell, Jerry Avorn, Nazleen F Khan, Aaron S Kasselheim
  BMJ Open; DOI 10.1136/bmjopen-2017-018320
- **Adaptive Designs for Clinical Trials of Drugs and Biologics: Guidance for Industry**
  U.S. Department of Health and Human Services: Food and Drug Administration

- **Randomization by minimization for unbalanced treatment allocation**
  Baoguang Han, Nathan H Enas and Damien McEntagart
  Statistics in Medicine; DOI 10.1002/sim.3710

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Thank you.

Step up to the microphone for any questions.

And thanks to the REDCap team at Vanderbilt University

Title: Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support

Author: Paul A. Harris,Robert Taylor,Robert Thielke,Jonathon Payne,Nathaniel Gonzalez,Jose G. Conde

Publication: Journal of Biomedical Informatics

Publisher: Elsevier

Date: April 2009

DOI: https://doi.org/10.1016/j.jbi.2008.08.010