Adapting Hitchings' code towards adaptive trials

Parameters we can change

- Number of communities (80)
- Average people per community (100)
- Probability of connection within community (0.15)
- Probability of connection between communities (0)
- Probability of connection with source (1)
- Size of population in source (50000)

Parameters we can change

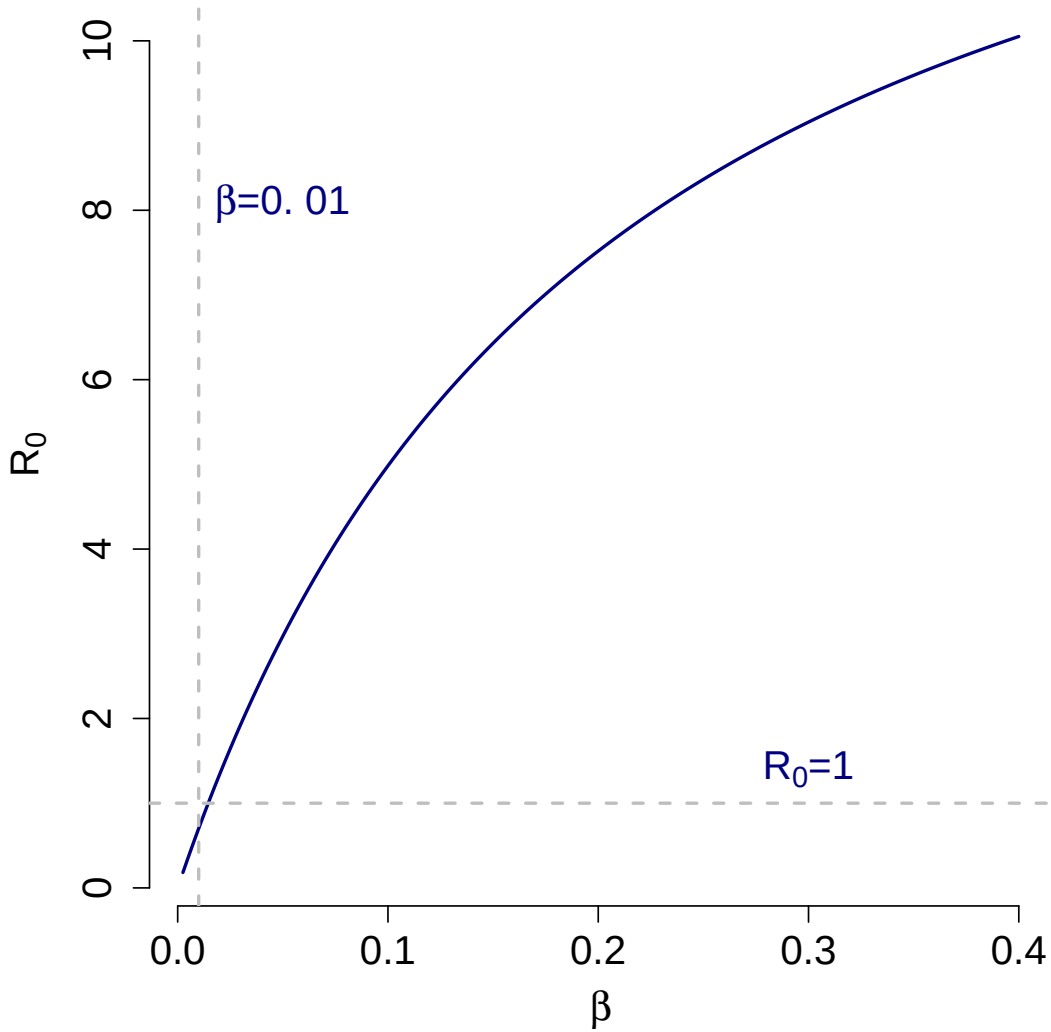
- Number of days of source infection (730)
- Trial start day (100)
- Trial duration (400)
- Enrollment and vaccination day (100)
- Enrollment probability (0.75)
- Vaccination probability (0.5)
- Vaccine efficacy (0.6)
- Average incubation period (10)

Parameters we can change

- Incubation period $\sim \Gamma$(shape=3.11, rate=0.32)
- Infection period $\sim \Gamma$(shape=1.13, rate=0.226)
- Infection rate $\beta = 0.01$
- $R_0 = 0.7019$

```
R0 <- (1-(infperiod_rate/(infperiod_rate+beta))^infperiod_shape) *
  (((ave_community_size-1)*(1-rate_within)*rate_within +
      (num_communities-1)*ave_community_size*(1-rate_between)*rate_between +
      ((ave_community_size-1)*rate_within + (num_communities-1)*ave_community_size*rate_between)^2)/
     ((ave_community_size-1)*rate_within + (num_communities-1)*ave_community_size*rate_between)-1)
```

R_0 as a function of β



What is β?

In the source population, β is the instantaneous rate of infection of a susceptible person S by an infectious person I:

$$\frac{dS}{dt} = -\beta S \frac{I}{N}$$

N is the whole population, so $p_I = \frac{I}{N}$ is the fraction of the population infectious.
Assuming t to be counting days, the probability for an individual to become infected on a given day is $\beta \times p_I$.

What is β?

In the community populations, β is the probability to be infected by your infectious neighbour. Let i, j be individuals in the network, and let $\mathcal{N}(i)$ be the set of neighbours of i. The probability for individual i to become infected on a given day (by one of their neighbours) is

$$\sum_{j \in \mathcal{N}(i)} \beta \text{ Prob}(j \text{ infected})$$

Assuming a homogeneous population, we could write this as

$$\begin{aligned} \sum_{j \in \mathcal{N}(i)} \beta \text{ Prob}(j \text{ infected}) &= \beta \sum_{j \in \mathcal{N}(i)} p_I \\ &= \beta \times \text{length}(\mathcal{N}(i)) \times p_I \\ &> \beta \times p_I \end{aligned}$$

What is β?

Hitchings chose $R_{\text{eff}} = 0.61$, $\text{length}(\mathcal{N}(i)) = 50$ and $t_{\text{inf}} = 2.94$ (*Mean infectious period in presence of daily probability detection 0.2*) to define

$$\beta = R_{\text{eff}}/\text{length}(\mathcal{N}(i))/t_{\text{inf}} = 0.01$$

from

$$R_{\text{eff}} = \int_0^{t_{\text{inf}}} \beta \ \text{length}(\mathcal{N}(i))dt$$

What is β?

- So, there are different values for β because one was chosen to match a particular choice of infection parameters (2017, 2018) and one was chosen to give a background input (2018).
- On top of having different values in the 2018 work, the βs also have different meanings (or contexts): the "random mixing" in the source population equates to "one interaction at a time". Individuals in the communities, on the other hand, have multiple (static) interactions.
- I propose we define β to be the probability to be infected by your neighbour, and add a term $f()$ in $\frac{dS}{dt} = -f()\beta S\frac{I}{N}$ to account for average connectivity in the source population.

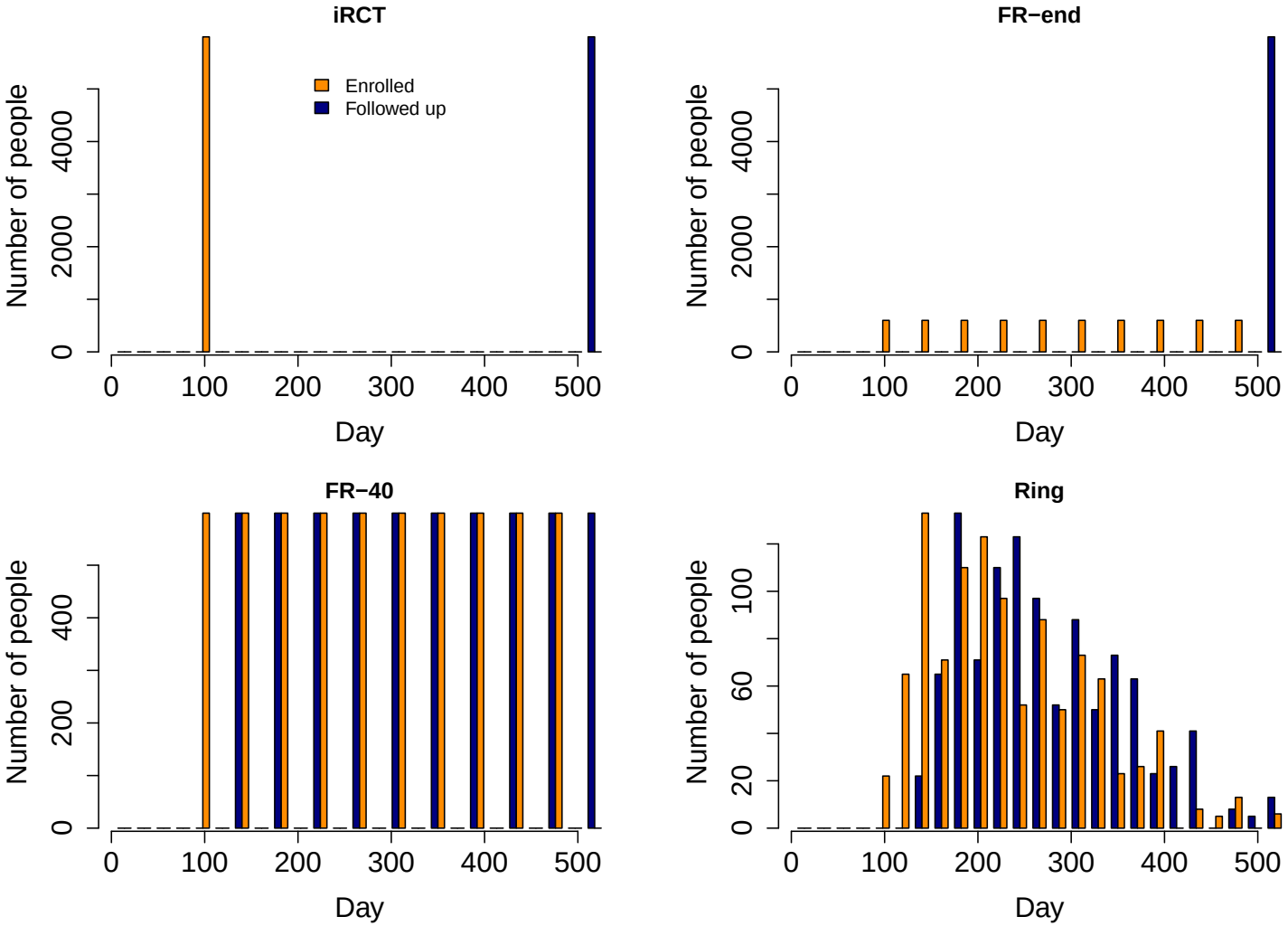
Summary of methods

	Instant	Staggered	Ring
Binary (fixed window)	iRCT/cRCT	FR-40/FA/TS	Ring
Binary (moving window)	–	FR-end	
Time to event	iRCT/cRCT		

Summary of methods

Method	Vaccination day(s)	Vaccination probability	End point
iRCT	100	0.5	Trial end
cRCT	100	0.5	Trial end
FR-end	100, 140,...,460	0.5	Trial end
FR-40	100, 140,...,460	0.5	40 days
FA	100, 140,...,460	Adaptive	40 days
TS	100, 140,...,460	Adaptive	40 days
Ring	100 onwards	0.5	40 days

Enrollment and follow up



Frequentist adaptive (FA) and Bayesian adaptive (Thompson sampling, TS)

- b = number of participants per stage = variable
- j = stage number = $1, ..., J$
- J = total number of stages
- T = total number of participants = $\sum_{j=1}^{J} b_j \neq Jb$?
- c = exponent for stage $j = \frac{jb}{2T} \rightarrow \frac{\sum_{i=1}^{j} b_i}{2T}$?
- Calculate:
  - p_0 = probability uninfected|control
  - p_1 = probability uninfected|vaccine
- Using:
  - FA (MLE): successes/(successes+fails)
  - TS: Uniform prior Beta(1,1); posterior Beta(1+successes,1+fails)
- Define allocation probability π_1 as:
  - FA (MLE): $\frac{R}{R+1}$ where $R = \sqrt{\frac{p_1}{p_0}}$
  - TS: $\frac{\Pr(p_1 > p_0)}{\Pr(p_1 > p_0) + \Pr(p_1 < p_0)} = \Pr(p_1 > p_0)$

Results: mean (standard deviation) for 500 simulations

Method	Cases	Vaccinations	Vaccinated cases	Cases/ vaccination	Power	Type I error	Vaccine efficacy
iRCT	125 (35)	3000 (38)	23.9 (8.2)	.042 (.012)	0.92	0.046	.57 (.11)
cRCT	170 (58)	3001 (57)	15.5 (7)	.057 (.019)	0.97	0.65	.81 (.13)
FR-end	192 (52)	2998 (38)	15.9 (6.3)	.064 (.017)	0.76	.048	.52 (.14)
FR-40	192 (52)	2998 (38)	15.9 (6.3)	.064 (.017)	0.12	0.052	.29 (.47)
FA	193 (53)	2997 (38)	15.9 (6.4)	.065 (.018)	0.15	0.052	.3 (.53)
TS	183 (53)	3780 (1100)	16.4 (6.6)	.058 (.046)	0.034	0.012	.32 (.49)
Ring	161 (39)	541.3 (99)	18.8 (8.2)	.3 (.033)	0.88	0.068	.59 (.13)

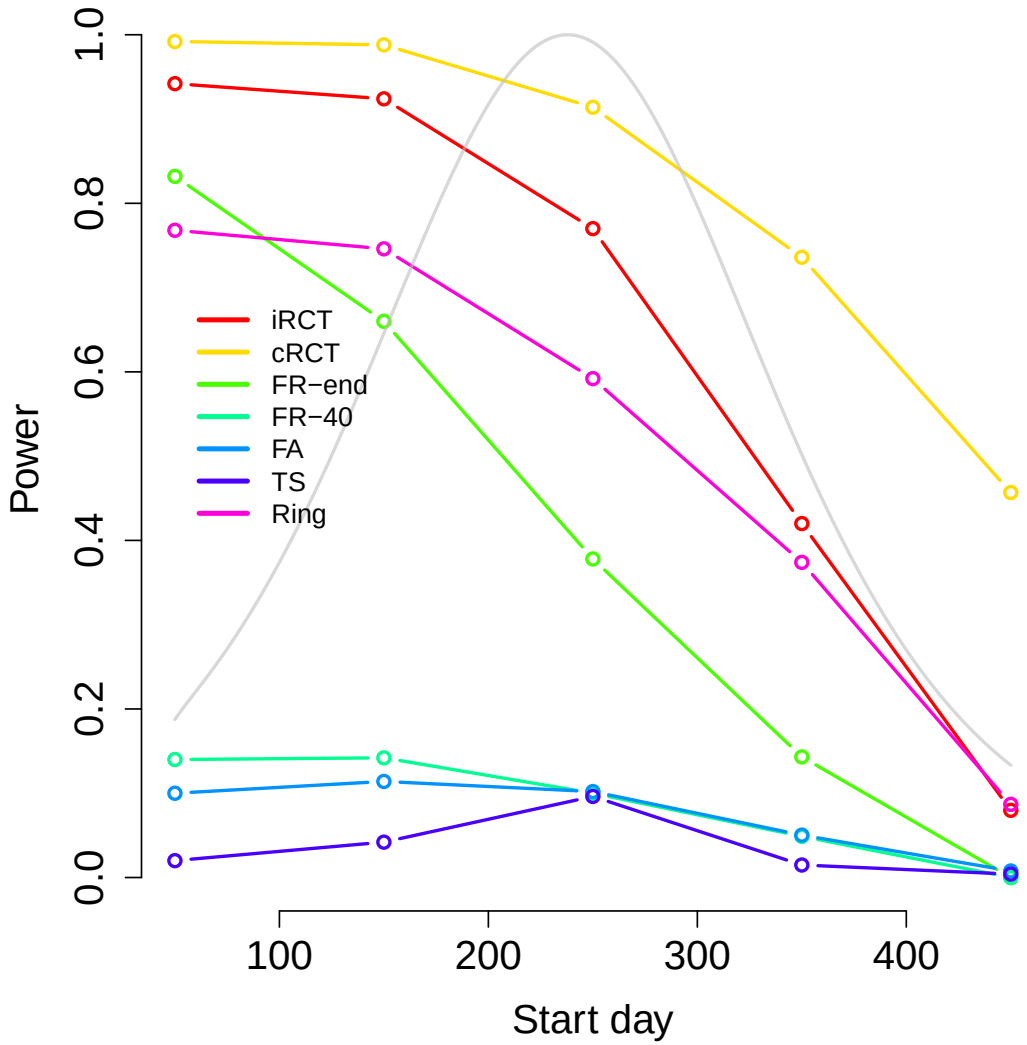
'Primary endpoint': a 'success' is 'not infected', and 'fail' is a person who is infected, at the end of the trial for iRCT, cRCT, and FR-end, and 40 days after treatment for FR-40, FA, TS, and Ring.

Power = fraction of p values < 0.05 for vaccine efficacy $= 0.6$.

Type I error = fraction of p values < 0.05 for vaccine efficacy $= 0$.

$p = \text{dnorm}(Z)$; $Z = \frac{p_1 - p_0}{\sqrt{\sigma_0 + \sigma_1}}$; $\sigma_i = \frac{p_i(1-p_i)}{N_i}$; $\text{N}_i = \text{successes}_i + \text{fails}_i$.

Power plots (75% enrollment, total duration of 500 days)



Ring vaccination trial, Ebola ça suffit, BMJ, 2015

- Randomisation to immediate or 21-day–delay vaccination
- Uses WHO contact tracing record (`https://www.who.int/csr/resources/publications/ebola/contact-tracing-during-outbreak-of-ebola.pdf`)
- Contacts and contacts of contacts
- Ring enrolled if 60% not currently enrolled
- Outcome = time to event (Cox proportional hazards model)
- Target: 190 rings, average size 50 (=9500 people), to get 90% power for VE=0.7
- Follow up at 3, 14, 21, 42, 63, and 84 days
- Secondary analyses: deaths, and infection of non-enrolled ring members

Ring vaccination trial, interim results, 2015 (Henao-Restrepo et al., Lancet)

- Outcome = binary at least 10 days post randomisation
- Randomised to vaccination and 21-day–delay vaccination
- In 111 days, 90 clusters randomised. 48 (4123) vaccinated, 42 (3528) not
- After ten days, no cases among vaccinated, 16 among not vaccinated.
- Case confirmed through PCR (Ebola response team)
- "α spending strategy"

Ring vaccination trial, final results, 2017 (Henao-Restrepo et al., Lancet)

- Outcome = binary at least 10 days post randomisation
- In 122 days, 98 clusters randomised. 51 (2119/4539) vaccinated, 47 (2041/4557) not
- 19 unrandomised rings, 1677/2745 vaccinated.
- No cases of vaccinated after 10 days, vs. 23 unvaccinated.

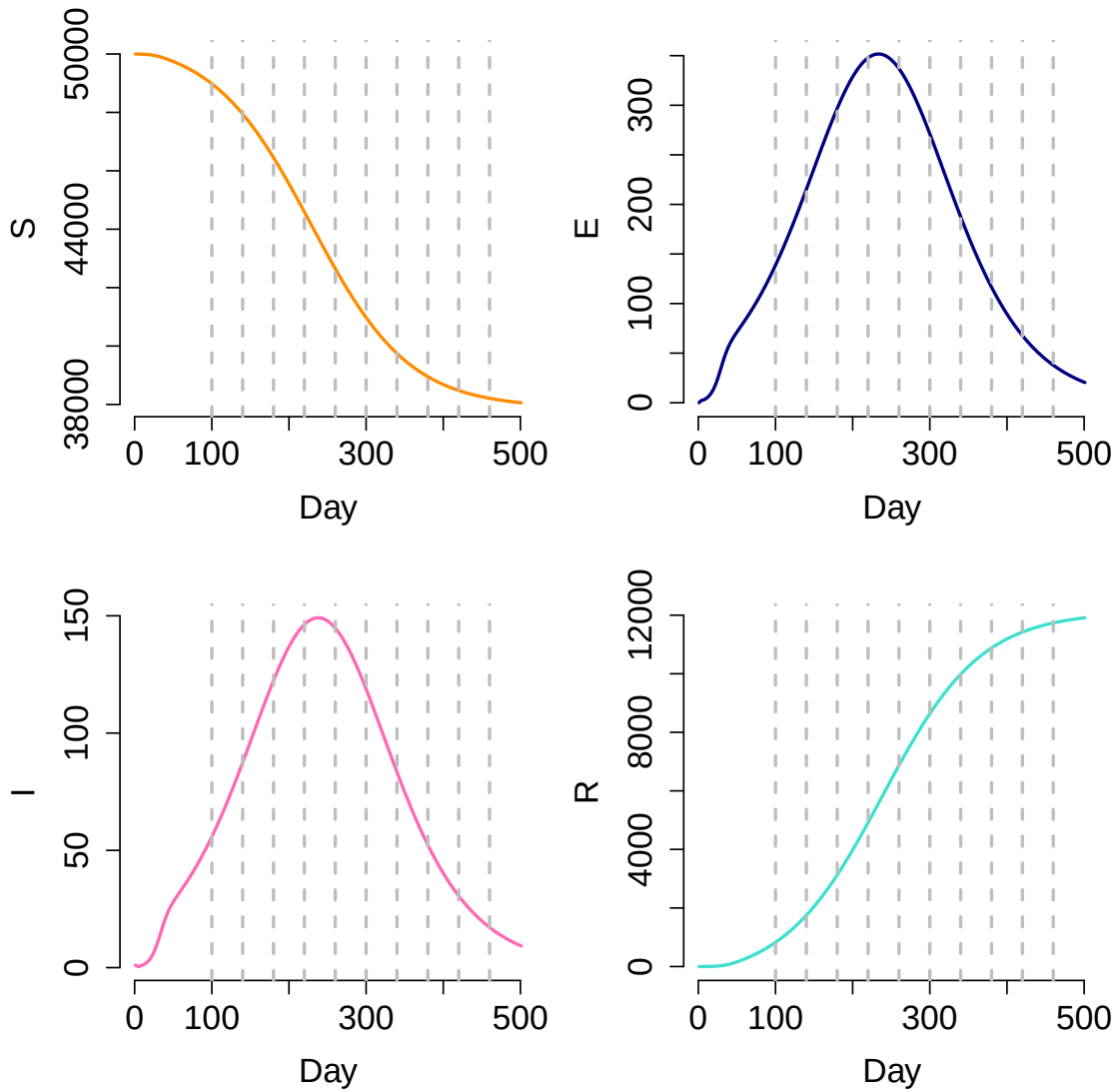
Ring vaccination (trial), 2017 (Gsell et al., Lancet)

- Outcome = binary at 21 days
- In 35 days, 1510 people were vaccinated (303 children; 307 front-line workers)
- Four rings, with numbers 715, 75, 484, and 385
- Time from inclusion to vaccination given: between 0 and 10 days
- Follow up at 30 minutes, and 3, 14, and 21 days

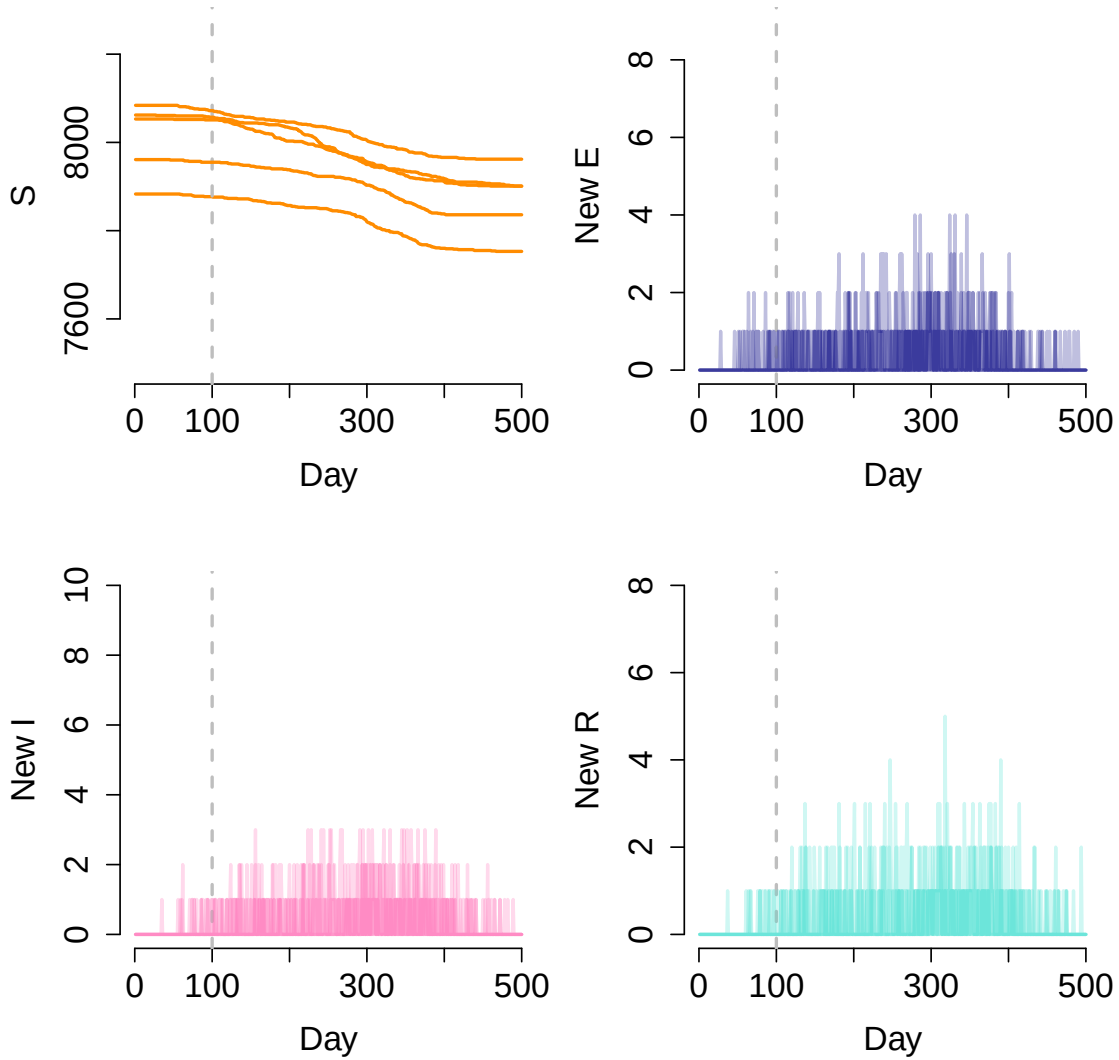
To do

- Discuss what temporal information we have and how we use it.
- Change enrollment so that it's more realistic. Ask Ben: what's realistic?
- Chris: what's the VOI for adaptive vs time to event?
- Revise the definition of π (e.g. include c, following development of enrollment schedule, which will allow the definition of j, b, J and T).
- Account for drift/trends in allocation probability calculation and final evaluation. The trend is coming from the source population's infection trajectory.
- Redesign the source population dynamics so that it depends in some way on our population's dynamics.
- Re Hitchings: why the source? Why the parameters and the community sizes?
- What are good parameters for communities and ebola dynamics?

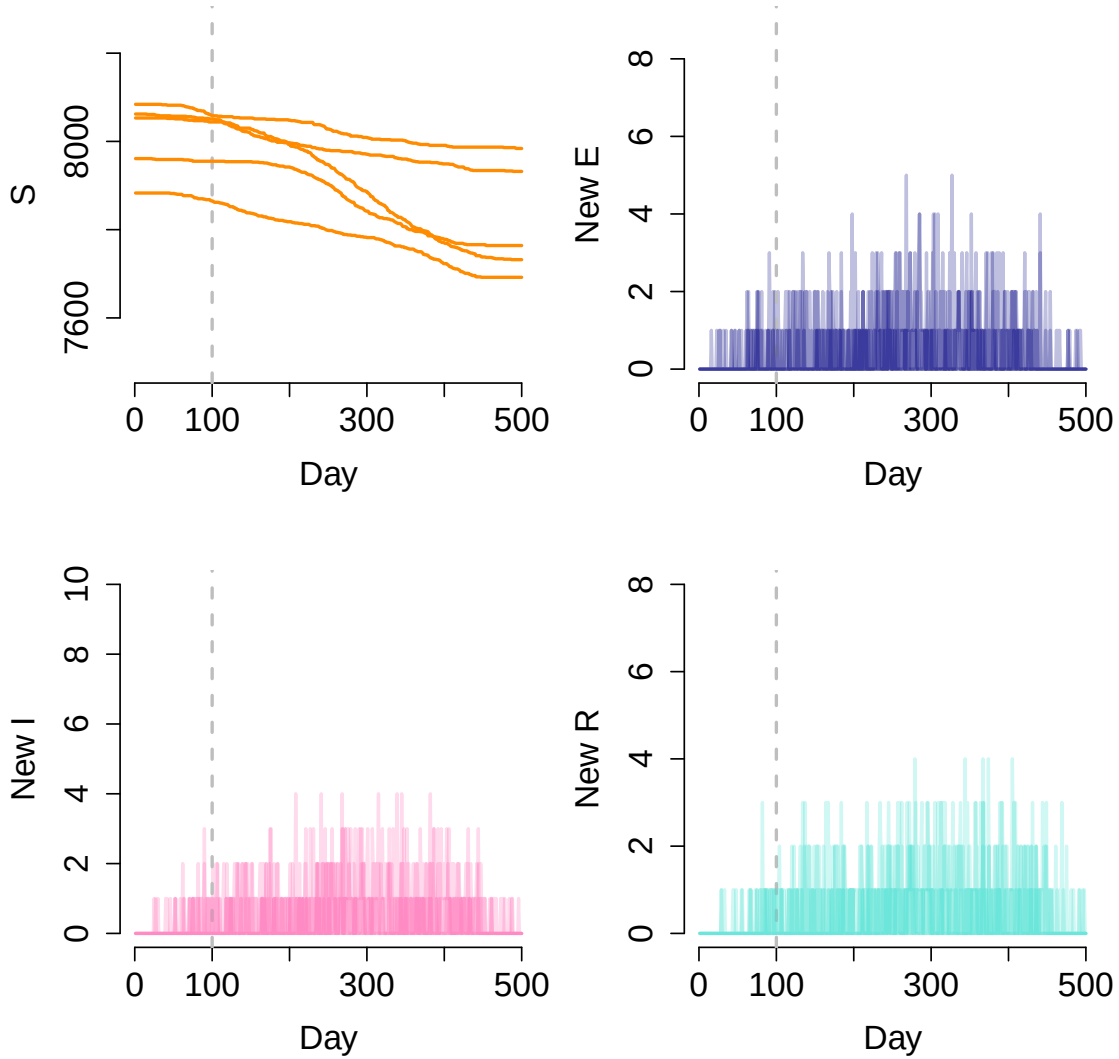
Source population



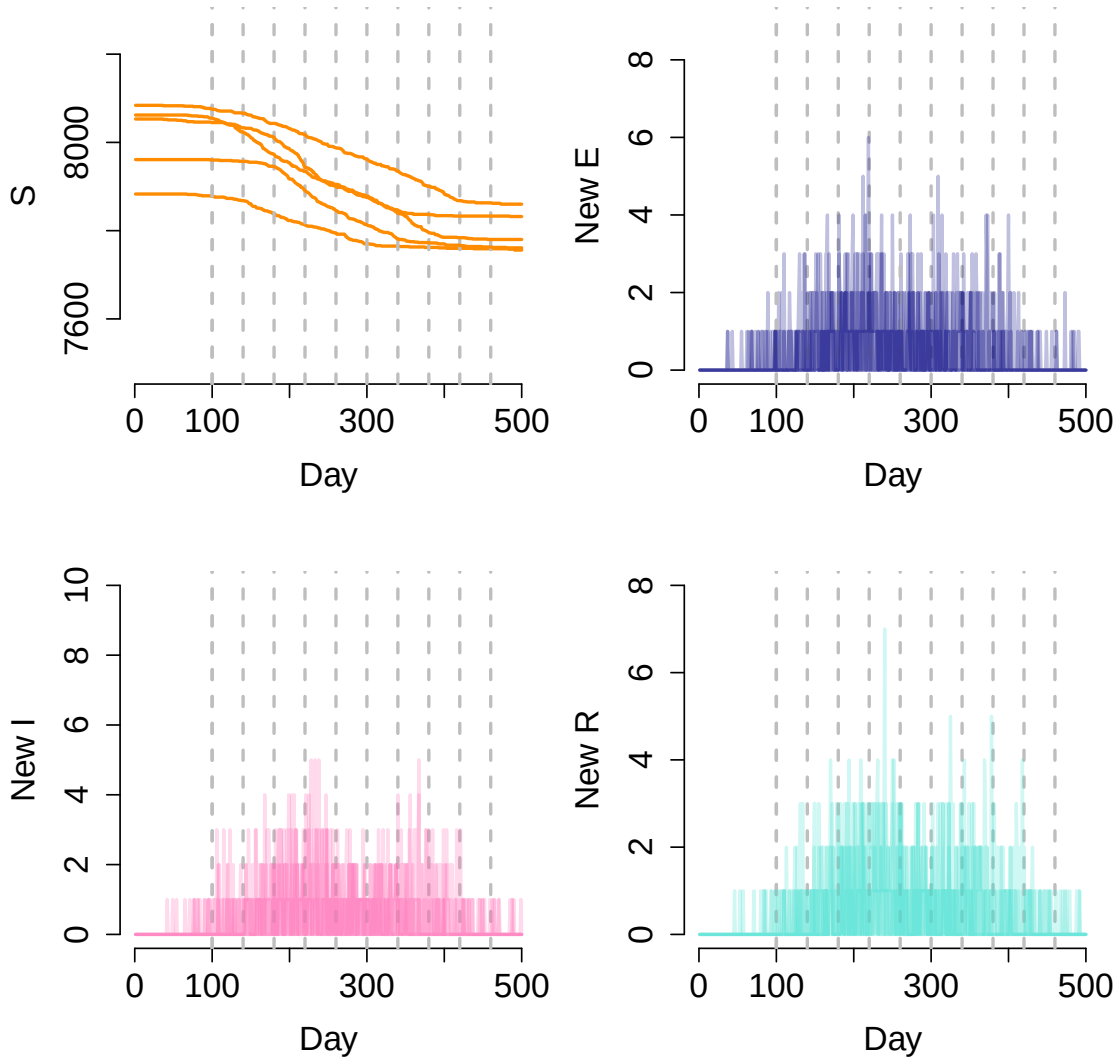
iRCT (5 samples)



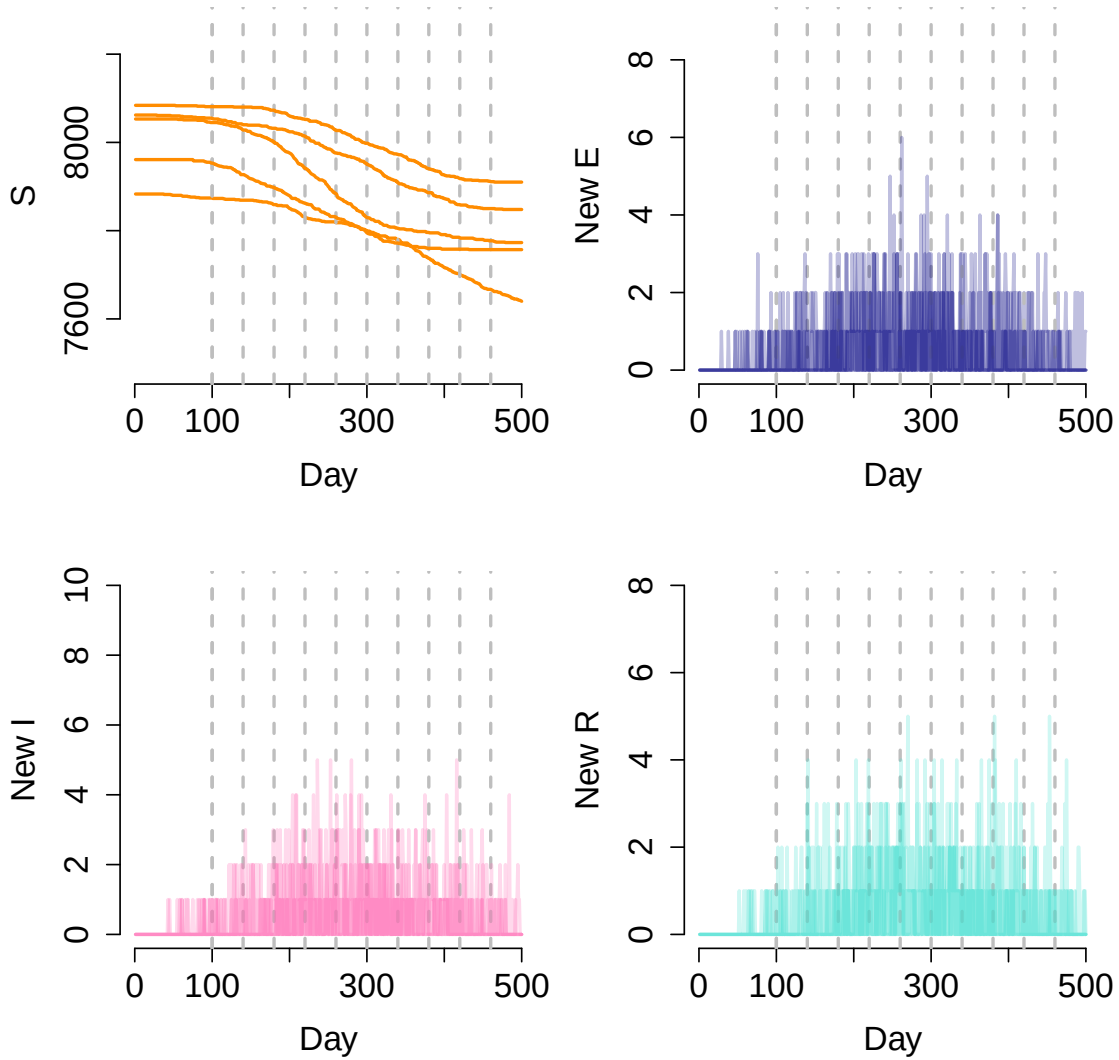
cRCT (5 samples)



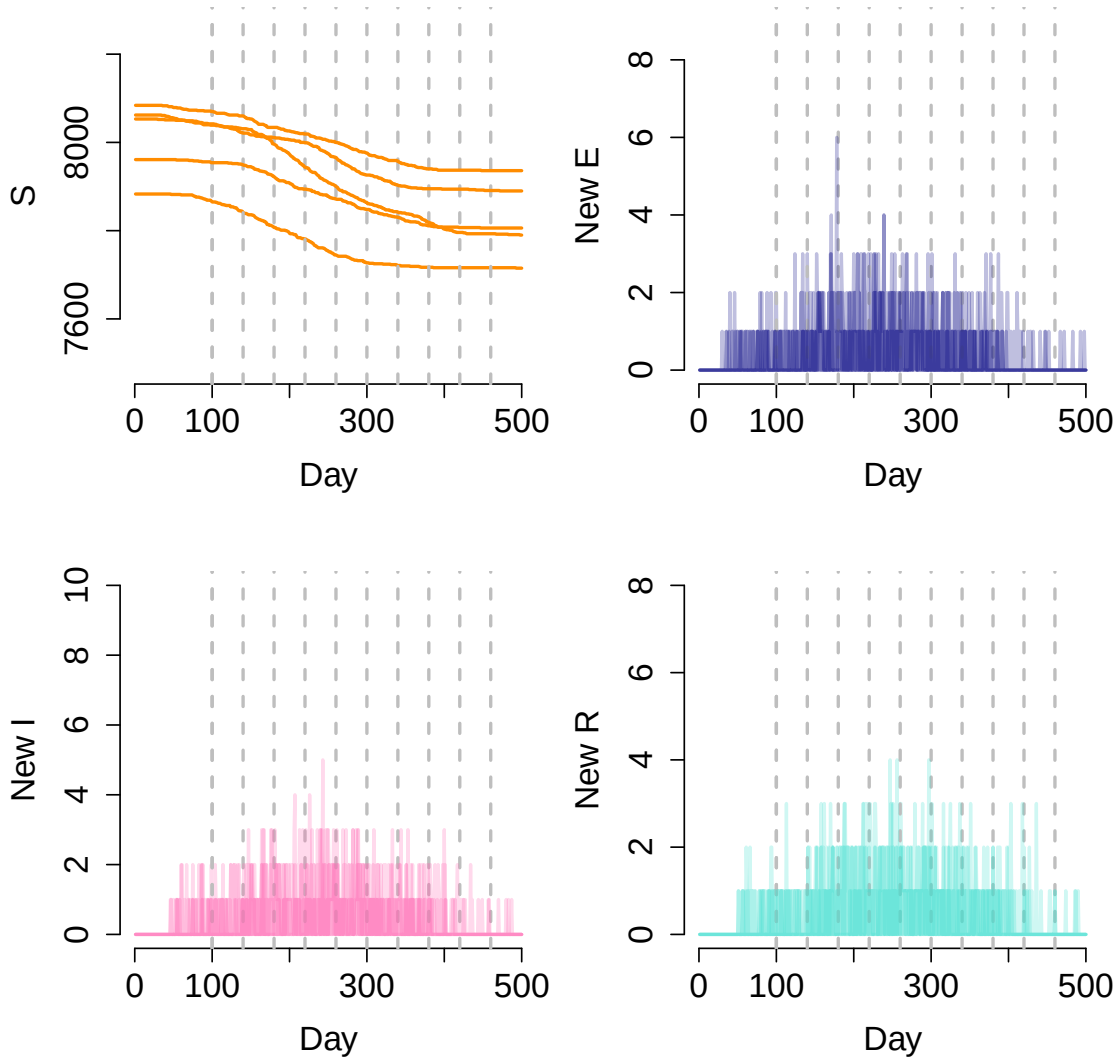
FR-iRCT (5 samples)



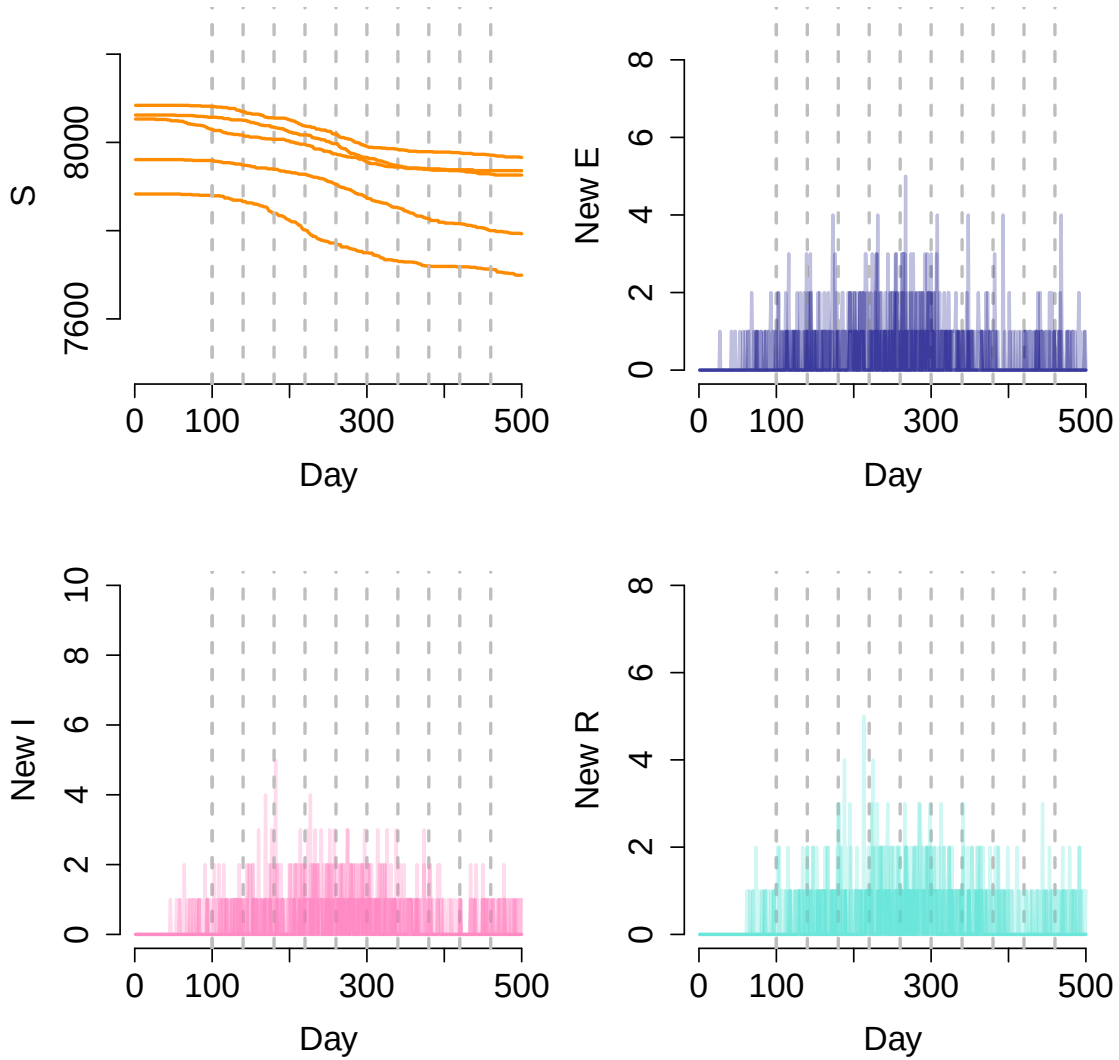
FA-iRCT (5 samples)



TS-iRCT (5 samples)



Ring (5 samples)



How many results do we get with a 40-day endpoint?