Increasing power of clinical trials in SCA1, SCA2, SCA3 and SCA6 with efficient designs and SARA scales

Emilien Petit, Sophie Tezenas and the Readisca consortium

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READISCA aims

- Establish the world's largest participant group of early-stage and symptomless SCA1 and SCA3 individuals

- Validate imaging signs in early stage and symptomless SCA1 and SCA3 individuals

- Adapt recent developments on statistical design and analysis of small population trials to future clinical trials for SCAs

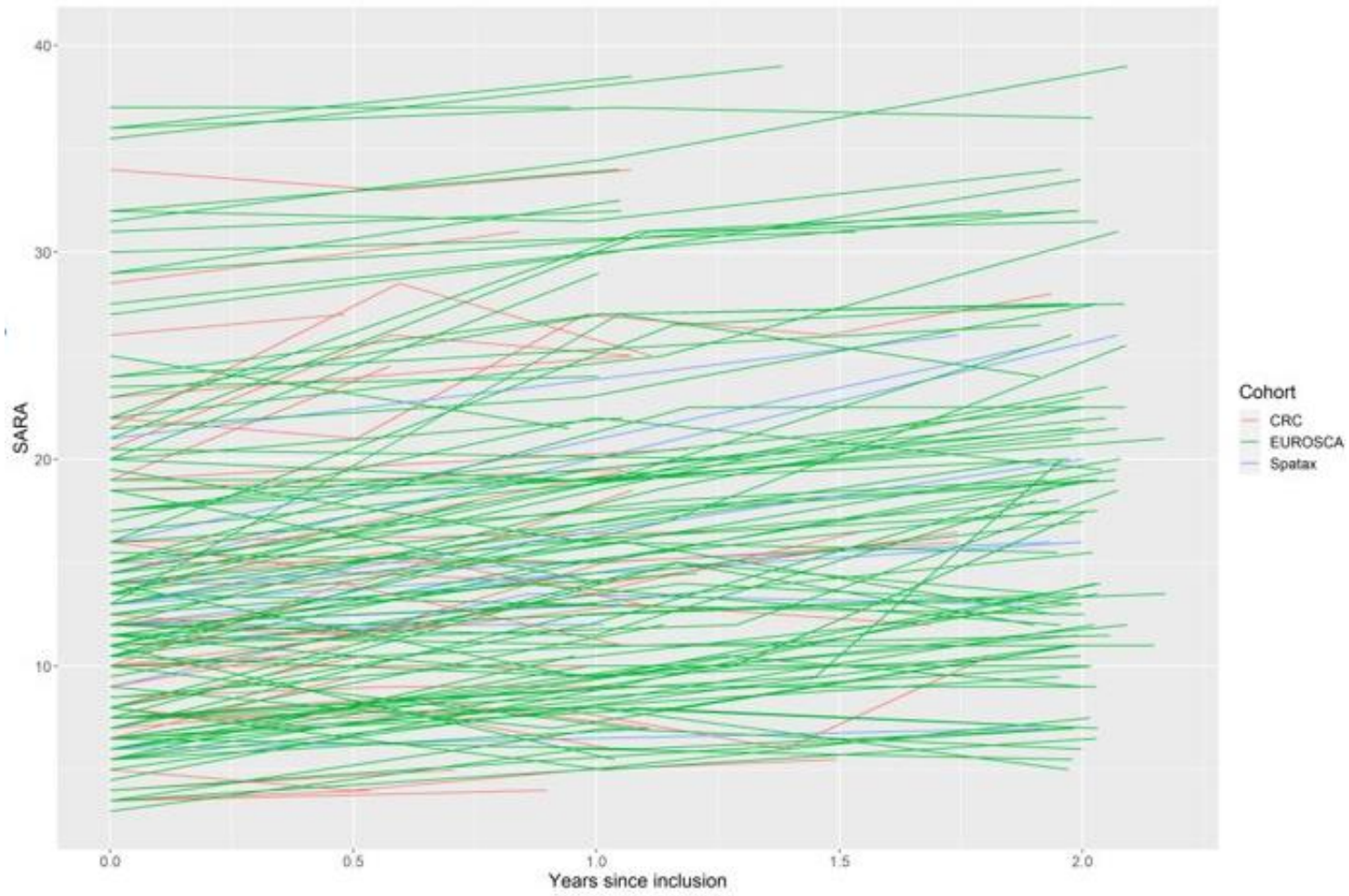
The data

3 cohorts :

- EUROSCA cohort : European patients
- CRC-SCA cohort : US patients
- SPATAX cohort : French patients

All visits with SARA within 2.25 years follow-up were kept

=> 1110 individuals, 2518 visits



SCA1 SARA individual progression

Institut du Cerveau ICM

SARA scales progression

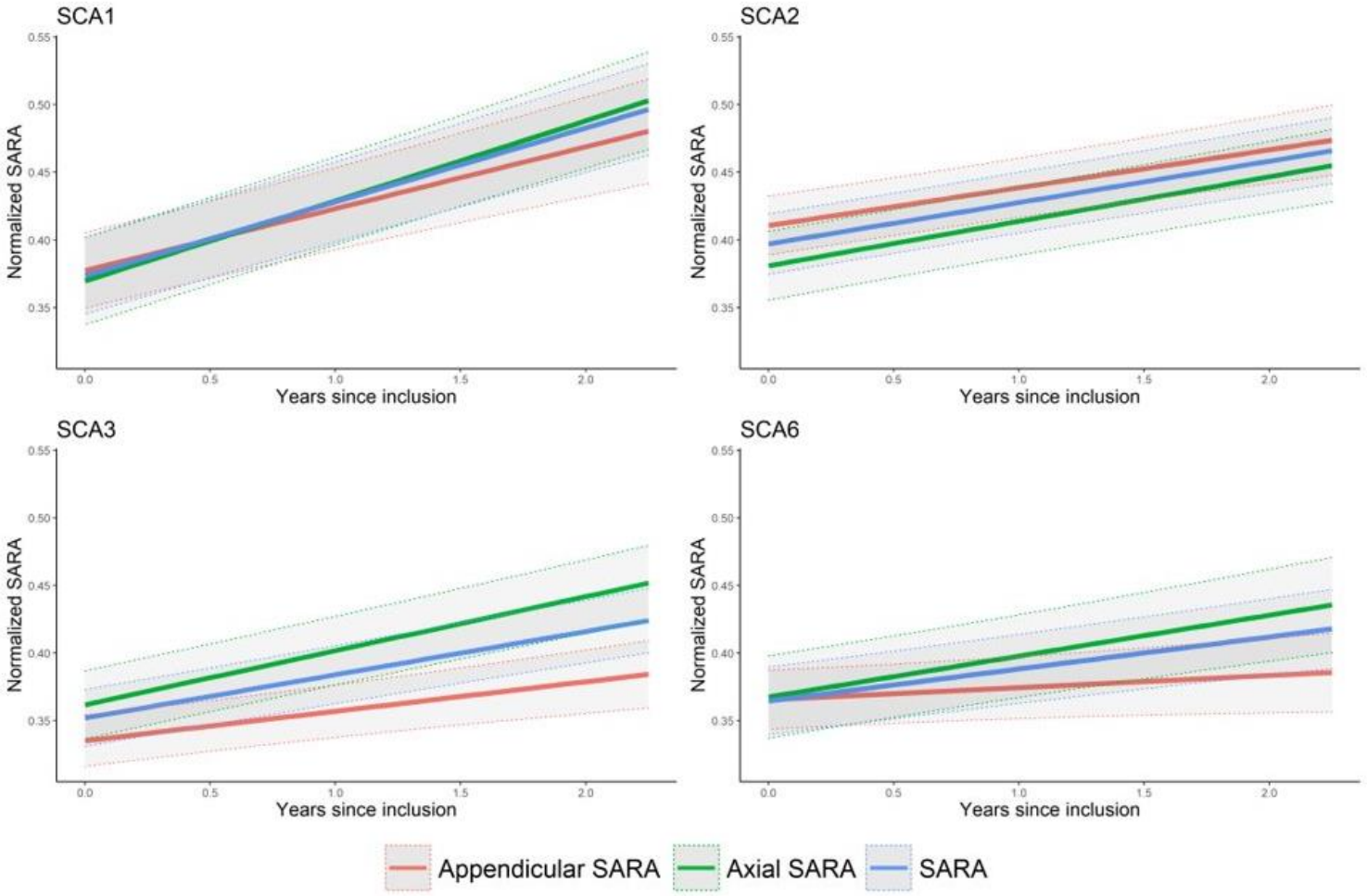
SARA : Full SARA, sum of all items (/40)

Axial SARA : sum of axial items (/24)

Appendicular SARA : sum of appendicular items (/16)

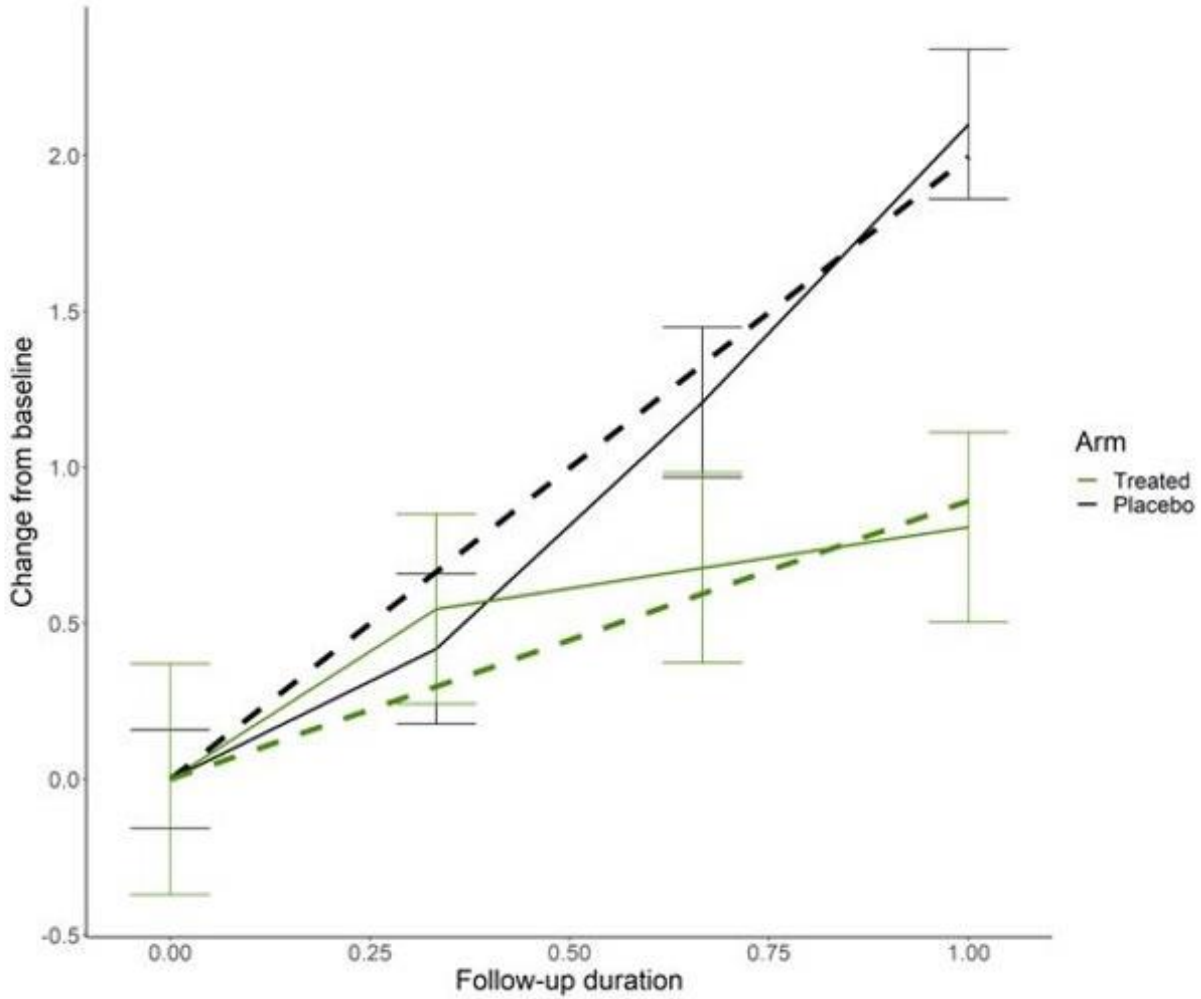
- All scale were normalized between 0 and 1
- Check for linearity
- Check for latent classes
- Linear mixed model by SCA

	SARA	Ax-SARA	Ap-SARA
SCA1	0.055 ± 0.004	0.059 ± 0.004 *	0.046 ± 0.006 *
SCA2	0.030 ± 0.003	0.033 ± 0.003	0.028± 0.004
SCA3	0.032 ± 0.003	0.040 ± 0.003 *	0.022 ± 0.005*
SCA6	0.023 ± 0.004	0.030 ± 0.005 *	0.009 ± 0.005* (p=0.069)



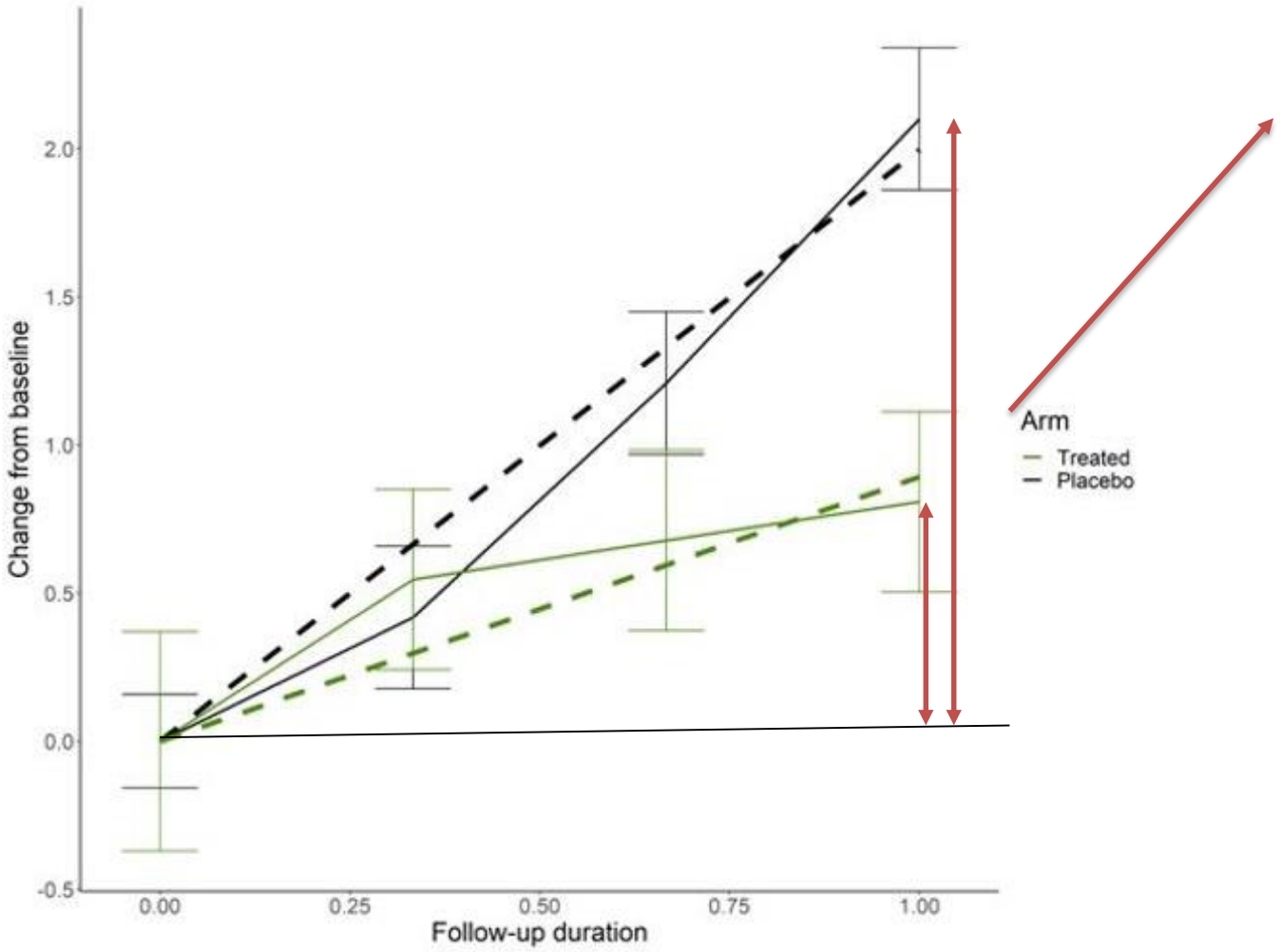
What to do with this to improve trials power?

Treatment effect measurment



Simulated clinical trial dataset

Treatment effect measurment



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- Comparison of mean change from baseline between groups (t.test) ?

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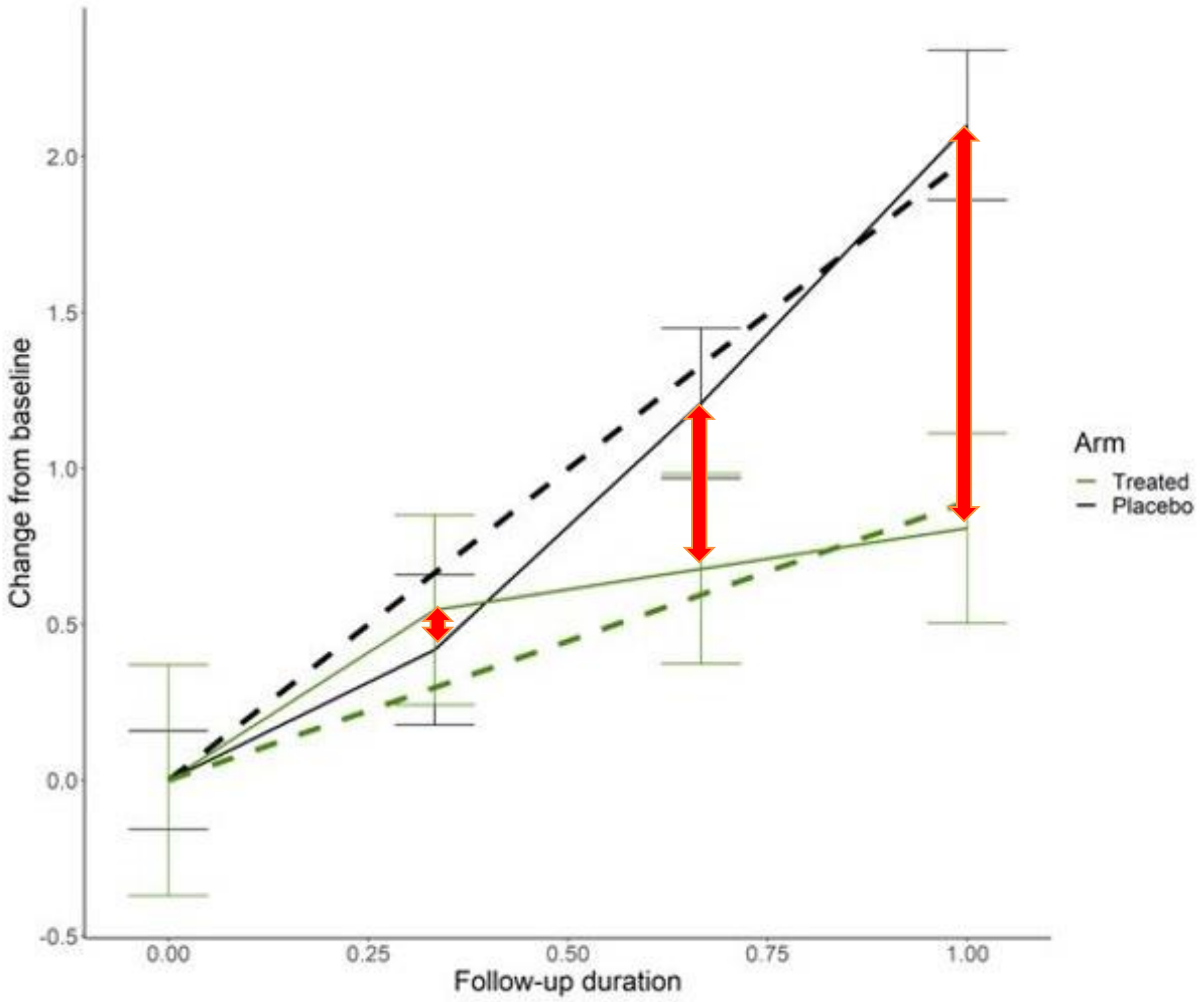

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- Mixed model for repeated mesures (MMRM)?

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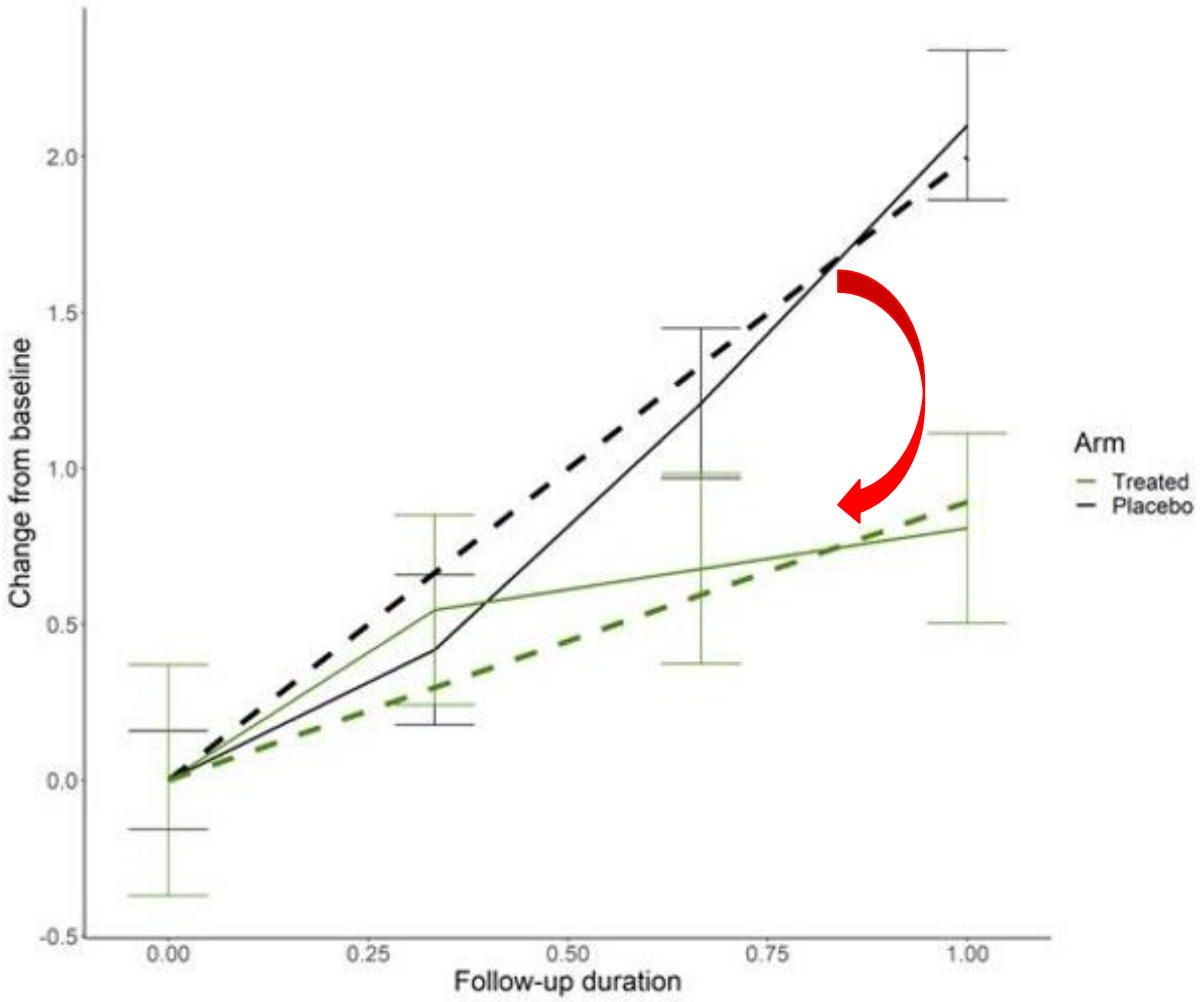

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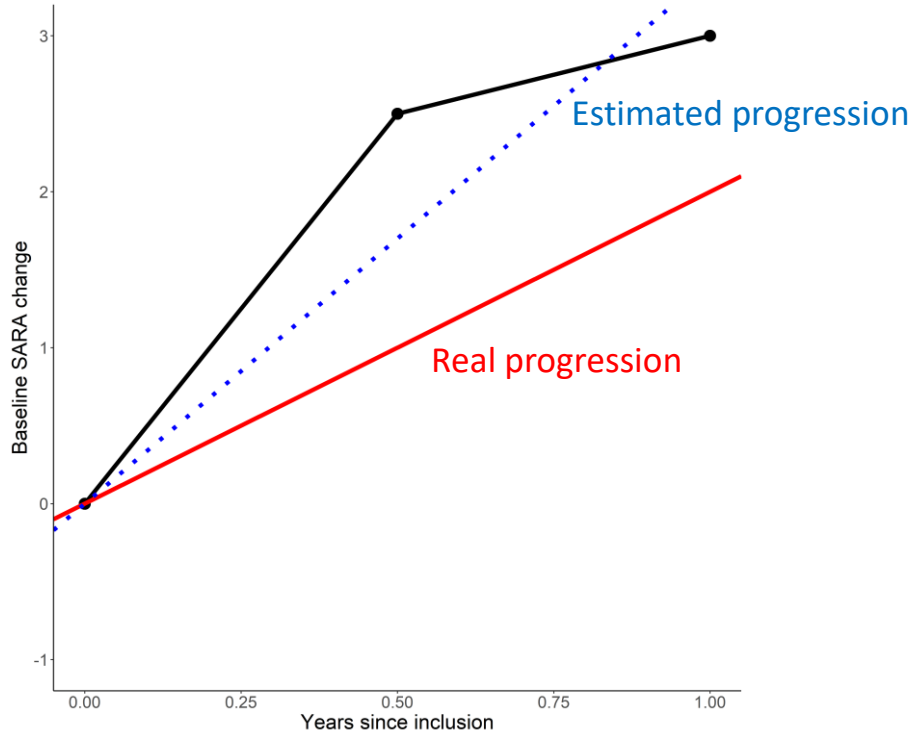
- Mixed model for repeated mesures (MMRM) ?
- Linear slope mixed model ?

Linear slopes mixed models



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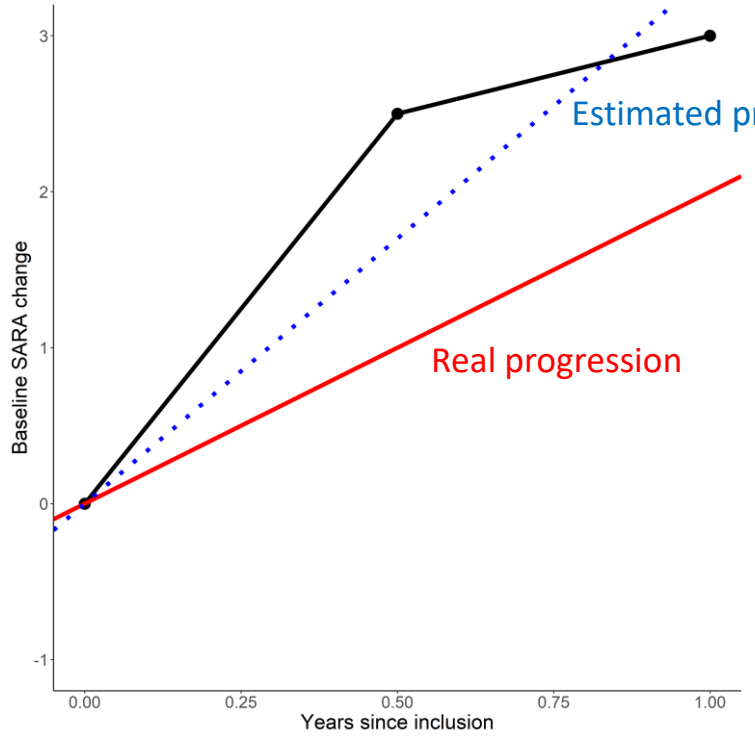
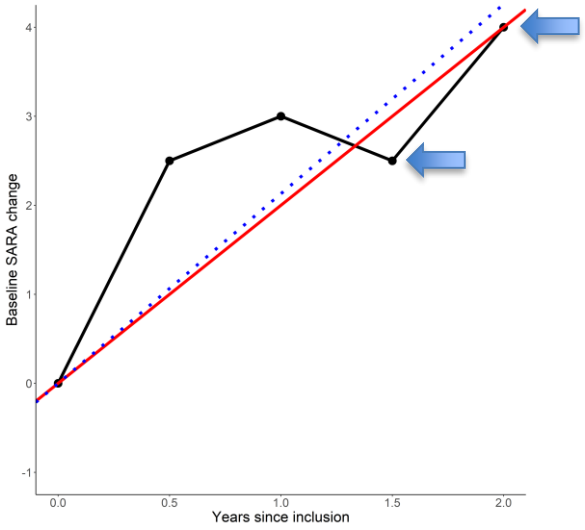


Add follow-up visits



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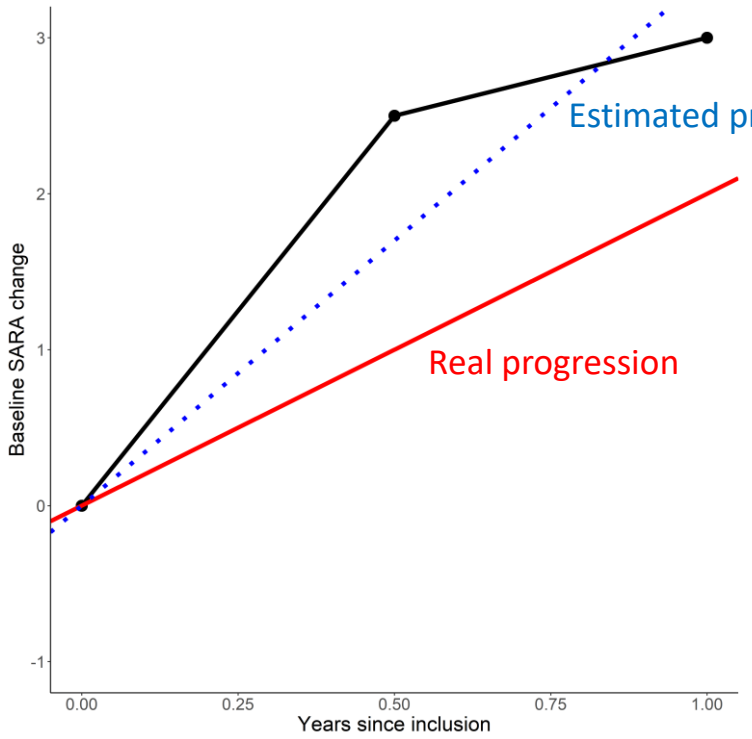
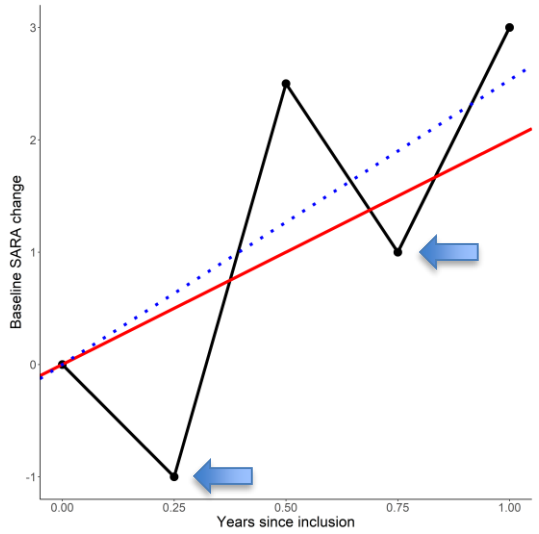


Add intermediate visits



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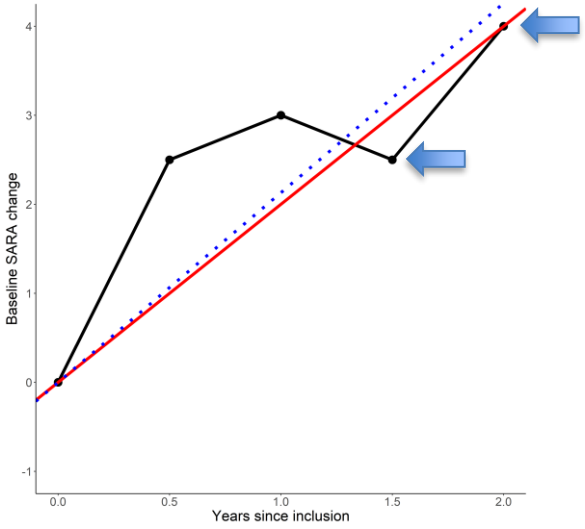

- Improving the estimation of the progression

Simulation studies : Follow-up duration

Simulating clinical trial datasets :

- Choose follow-up duration, number of visits (equally spaced), number of patients, treatment effect

- Randomly generate individual slopes and intercepts following SCA1 SARA progression

- Apply treatment effect on individual slopes in the treatment group

- Add noise equal to mean residual error of SCA1 SARA model

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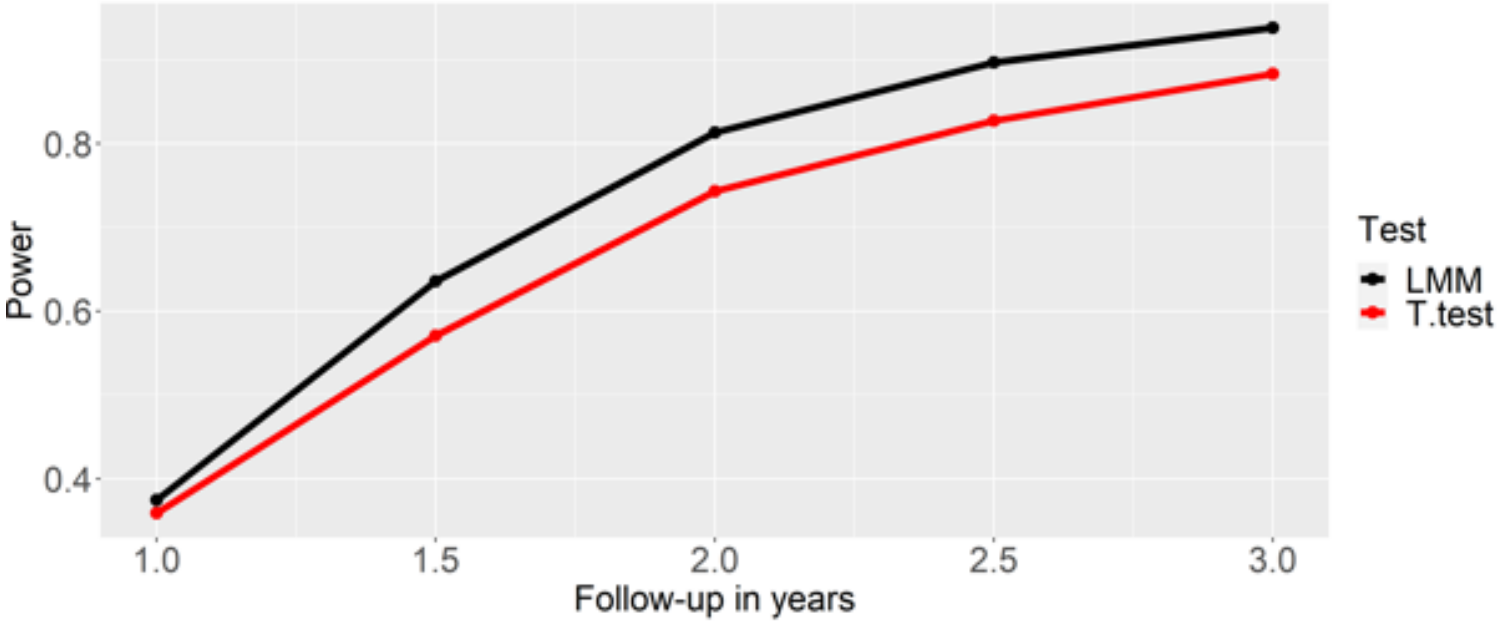
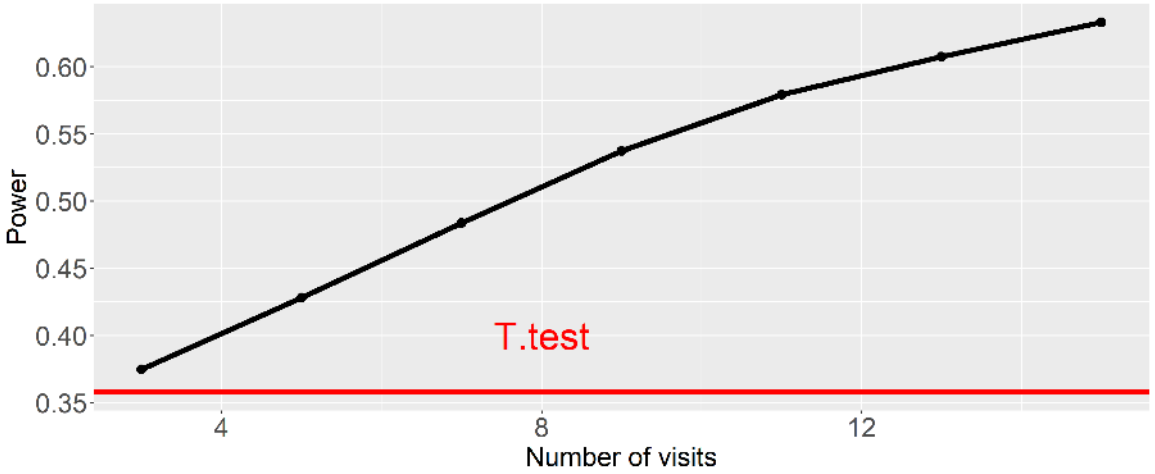


Power with a treatment effect of 50% reduction on slope with 30 participants in each arm and visits every 6 months. Parameters are taken from SCA1 SARA progression.

Simulation studies : Number of visits



Powers for a 1-year trial with 30 participants in each arm and 50% treatment effect

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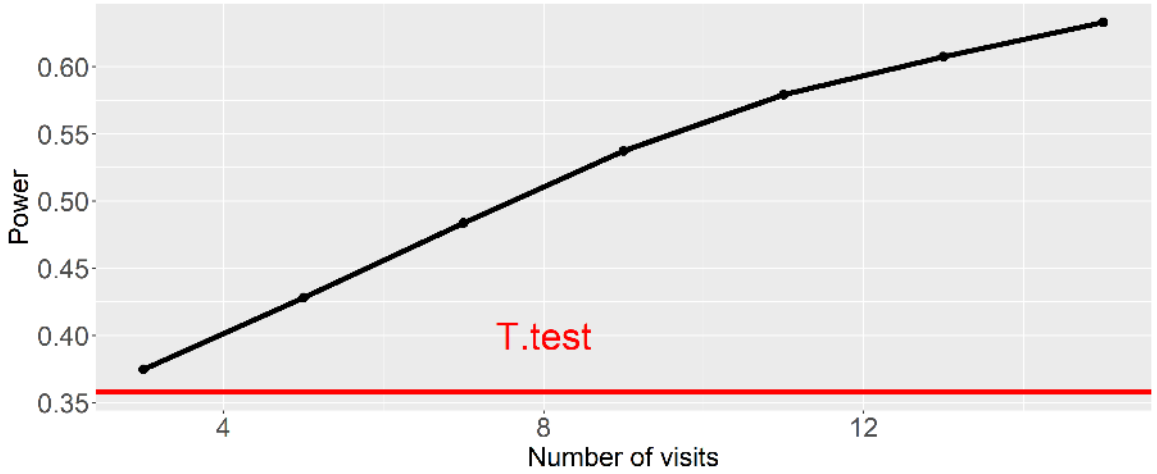

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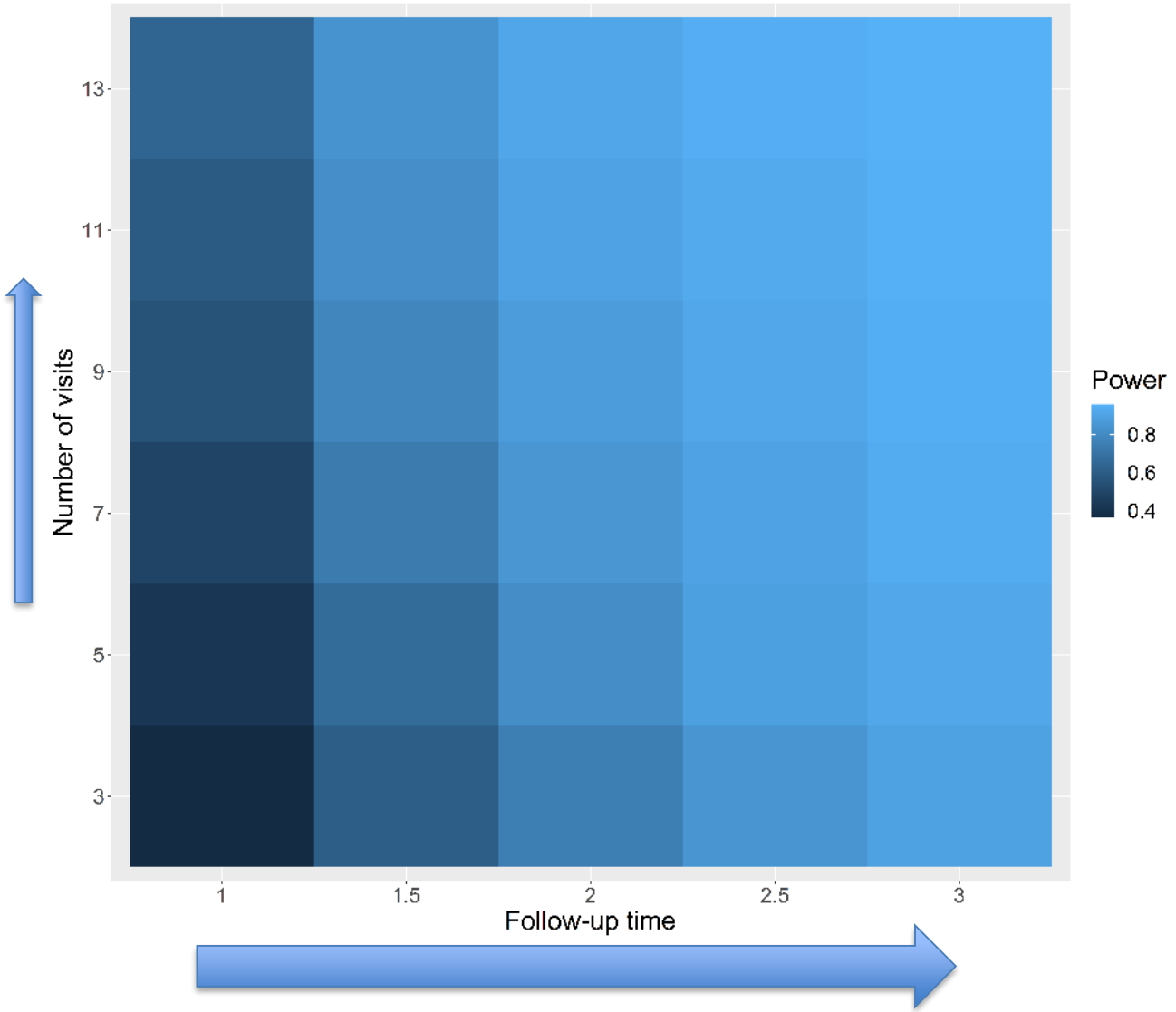

- Follow-up time as a greater impact than number of visits on power

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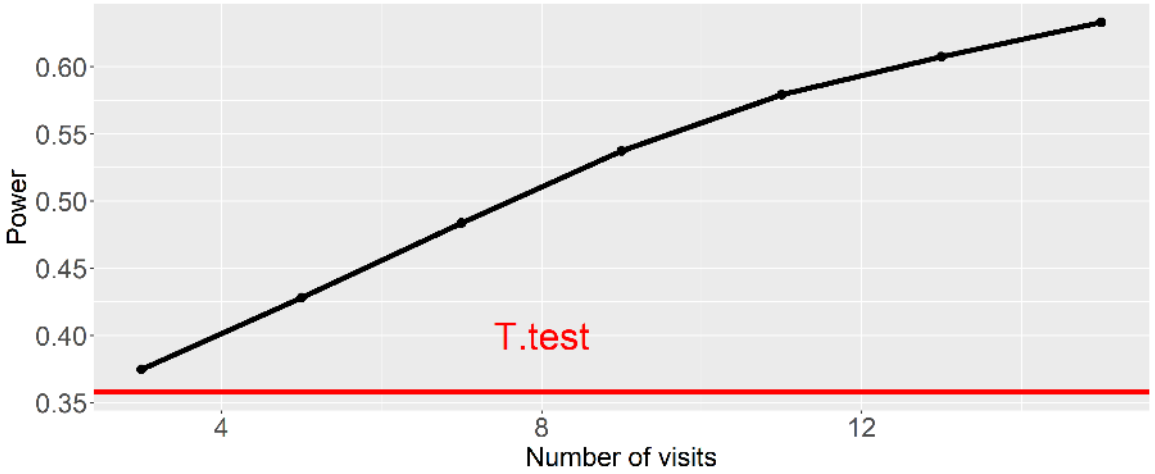
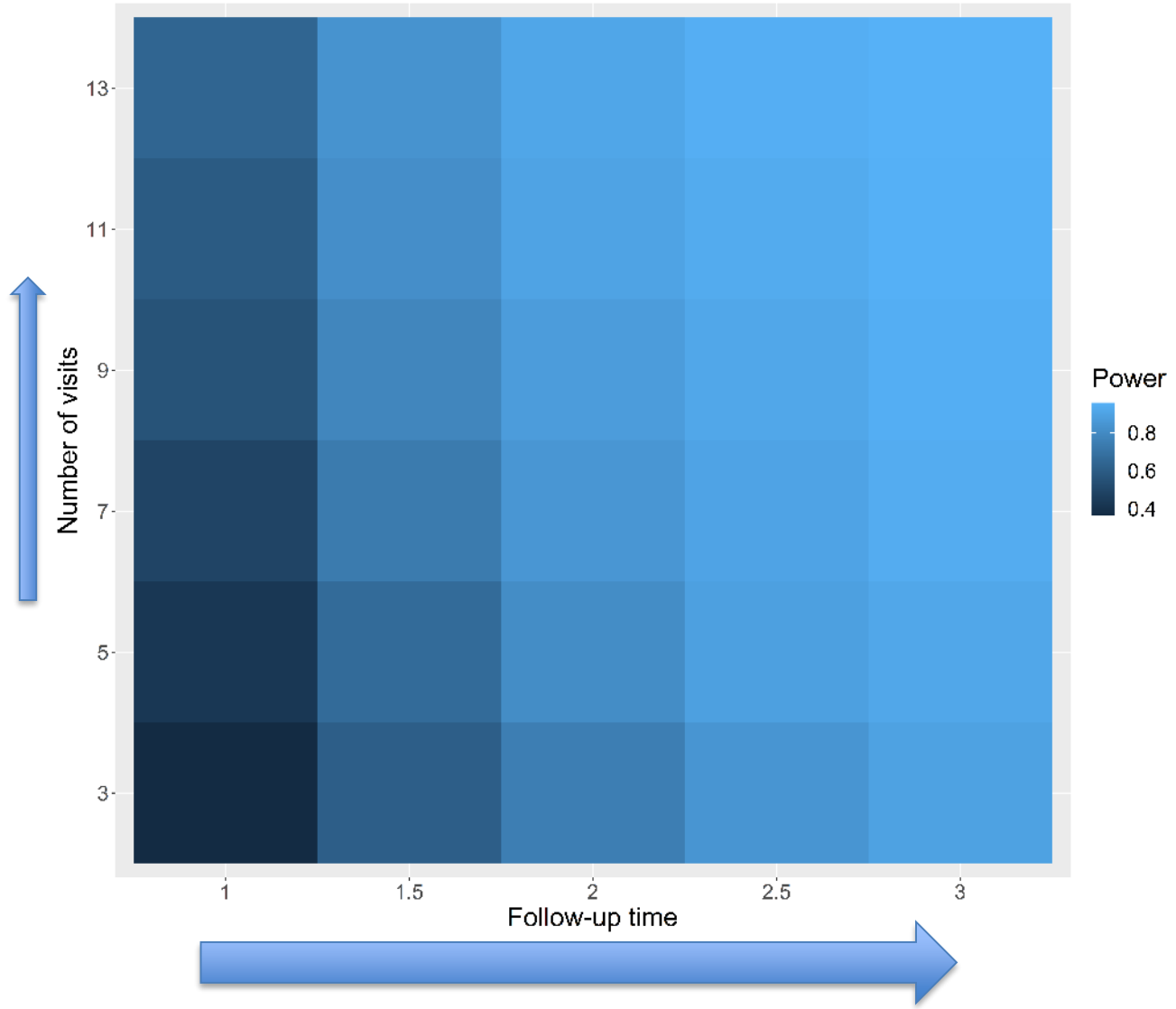


Powers for a 1-year trial with 30 participants in each arm and 50% treatment effect

	SARA	Ax-SARA	Ap-SARA
SCA1	34	35	102
SCA2	65	80	198
SCA3	58	52	>200
SCA6	180	>200	>200

Sample size for a 2 years trial to reach 90% power



- Follow-up time as a greater impact than number of visits on power

Discussion and conclusion

Conclusions :

- Axial SARA seems to have similar power than full SARA
- Increasing the number of visits whithin the same trial duration increases power.
- This increase is less efficient than increasing the follow-up duration

Aknowledgments

Cohorts PIs

Thomas Klockgether for the EUROSCA consortium

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Readisca statistical team

Sophie Tezenas du Montcel

READISCA
Clinical Trial Readiness for SCA1 and SCA3