

An approach for reducing the sample sizes of pediatric trials in Type 2 Diabetes Mellitus: longitudinal analysis versus standard analyses.

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Introduction

Objectives: Recruitment for pediatric trials in Type II Diabetes Mellitus (T2DM) is very challenging (1), necessitating the exploration of new approaches for reducing the sample sizes. In this work we assess if a longitudinal Non-Linear-Mixed-Effect (NLME) analysis of T2DM trial results could be more powerful and so require less patients than standard analyses.

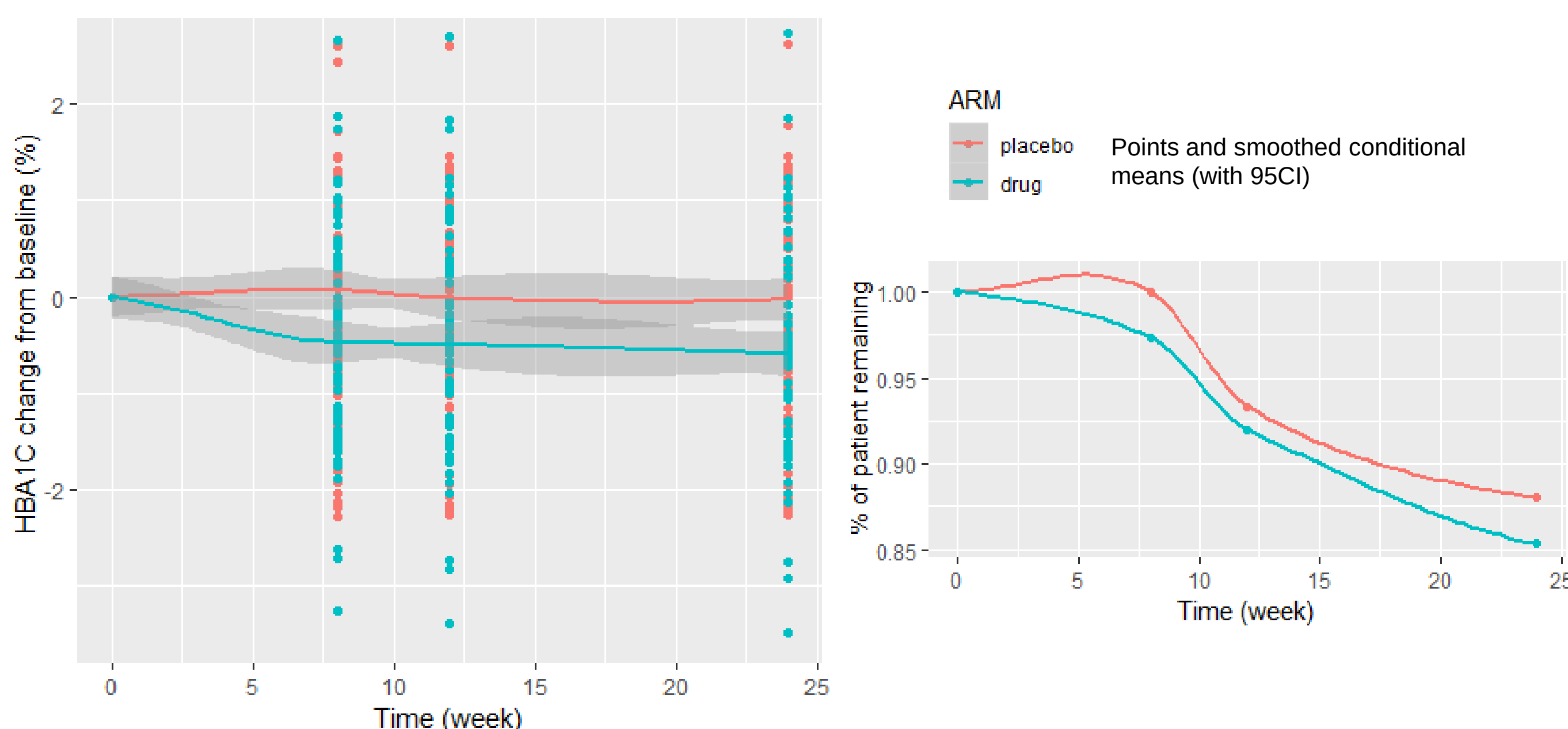
Method

- Simulation of studies in T2DM, with glycated hemoglobin (HbA1c) as main endpoint, 24 weeks duration, 2 arms, 75 patients per arm, HbA1c measurements at 0, 8, 12 and 24 weeks as common practice in T2DM trials, assuming a mean placebo effect of -0.1% HbA1c and a mean treatment effect of -0.5% HbA1c, and assuming inter-individual-variability (iiv)
- 3 scenarios: 2 with a structured model of negative exponential progression with steady state reached at week 12 (A) or week 20 (B), and an unstructured scenario (C)
 - Structured model
$$HbA1c_{t,i} = HbA1c_{baseline,i} + effect_{placebo,i} \cdot (1 - \exp(-k_{pi} \cdot t)) + effect_{drug,i} \cdot (1 - \exp(-k_{di} \cdot t)) + \varepsilon_{t,i}$$
 - Unstructured model shape
$$HbA1c_{t,i} = HbA1c_{baseline,i} + (-0.55)_{t=8W} + (-0.65)_{t=12W} + (-0.60)_{t=24W} + (1 - \exp(-0.20 \cdot t)) \cdot \eta_i + \varepsilon_{t,i}$$
- Dropout rate modeled through a logistic model; probability P of dropout increases with time and bad efficacy (with MAR phenomenon); higher baseline rate assumed in treated arm (more adverse events); global dropout rate of 10% at W24
- Simulation of N=1000 trials & power of each type of analysis computed as the % of the N trials with statistical significance of a between-group difference in HbA1c change from baseline at week 24 for each type of analysis:
 - LOCF + ANOVA at week 24
 - Mixed-effects Model Repeated Measures (MMRM) approach
 - Longitudinal NLME modelling, using the structured Hba1c model with iiv only on placebo effect, then prediction of treatment effect at week 24 assuming steady state is reached

Results

Simulations: consistency was checked.

Fig. 1. Example of 1 trial simulation of 75 patients per arm - scenario B



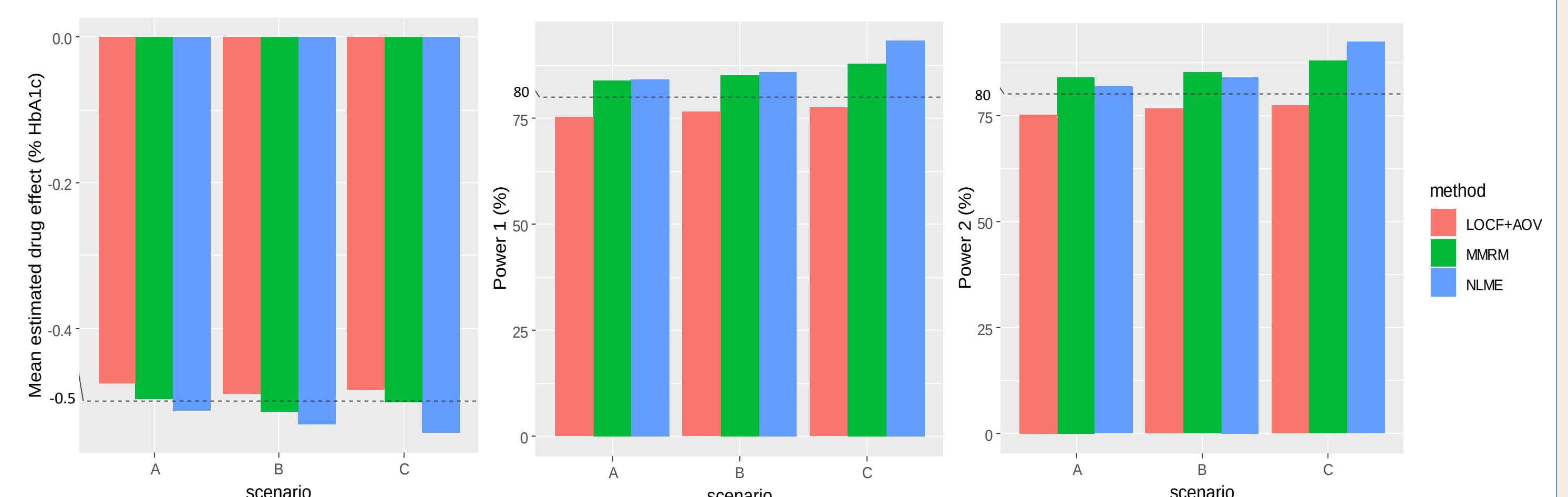
Comparison of the 3 methods (Table 1, Fig.2)

- LOCF + ANOVA analysis slightly under-estimated magnitude of drug effect and was less powerful than MMRM and NLME analyses in all scenarios
- For scenarios A & B, similar power observed between MMRM and NLME analyses, and for scenario C, NLME analysis a little more powerful but associated with a slight overestimation of magnitude of drug effect
- Slightly more precise estimation of drug effect parameter obtained with NLME method (better SE)

Table 1. Comparisons of methods on 1000 simulations

SCENARIO	Method	Mean estimated drug effect (% HbA1c)	Mean bias ^a (% HbA1c)	Empirical SE of estimated drug effect (% HbA1c)	Power1 (trial test considered missing when bad convergence)	Power2 (trial test considered non significant when bad convergence)	Number of trials with good analysis convergence
A	LOCF+AOV	-0.476	0.024	0.179	75.2%	75.2%	1 000
	MMRM	-0.497	0.003	0.186	83.9%	83.9%	1 000
	NLME	-0.516	-0.016	0.172	84.3%	79.3%	941
B	LOCF+AOV	-0.490	0.010	0.181	76.6%	76.6%	1 000
	MMRM	-0.515	-0.015	0.186	85.1%	85.1%	1 000
	NLME	-0.532	-0.032	0.172	85.7%	82.9%	967
C	LOCF+AOV	-0.484	0.016	0.181	77.5%	77.5%	1 000
	MMRM	-0.502	-0.002	0.189	87.9%	87.9%	1 000
	NLME	-0.545	-0.045	0.163	93.2%	91.9%	986

Fig. 2. Comparisons of methods on 1000 simulations



Further explorations

- Type 1 error a little inflated for MMRM & NLME (9 & 7-10%)
- Addition of HbA1c measurements at 4 and 52 weeks led to a gain in power for NLME compared to MMRM especially for scenarios B & C (gain ~ +8%)

Conclusions

The longitudinal modelling analyses MMRM and NLME were more powerful than the LOCF + ANOVA analysis at week 24. The NLME analysis gave slightly more precise drug effect estimations than the 2 other methods, however, it tended to overestimate the magnitude of drug effect and it was more powerful than standard MMRM analysis only for some scenarios; the gain in power was increased in presence of additional Hba1c measurements at early and late times.

→ Those results suggest that NLME analyses may help to reduce the required sample sizes in T2DM pediatric studies, provided that more assessments are planned and the study duration is increased.

References

- [1] Nadeau KJ, et al. Youth-Onset Type 2 Diabetes Consensus Report: Current Status, Challenges, and Priorities. *Diabetes Care*. 2016 Sep; 39(9):1635-42.