Lessons from "Failed" Pediatric T2DM Trials:

Bayesian Approach for Optimized Pediatric Trials

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Scope:

- **Analysis of "Failed" Pediatric Trials : Glimiperide, Glyburide, Rosiglitazone**
- **Design considerations for Pediatric T2DM trials**
- **Optimized Pediatric T2DM through Bayesian Approach**

Note: Some of the numbers in this presentation may have minor errors as they were consolidated from multiple sources for which important details may have been missed.

Glimepiride: Design

- Study: 26-Wk (2 wks screening + 24 Wk treatment) active-controlled (metformin) monotherapy non-inferiority study in 150 children 8 – 18 yrs old
  - NI margin: 0.3% with assumed SD of 1.2
- Major Inclusion: 7.1 <HbA1C<12.0 after 2Wk stabilization period
- Treatment:
  - glimepiride 1mg daily titrated every 4 wks for up to 3 visits (Wk 12) by doubling dose until mean fasting SMBG<7.0 mmol/L
  - metformin 500 mg bid titrated only at Wk 12 to 1000mg bid
- 1^{o} Endpoint: CFB HbA1c to Wk 24

Glimepiride: Result

	Glimepiride		Metformin	
Baseline	8.57 (1.3)		8.69 (1.4)	
Change from baseline (adjusted)	-0.95 (0.4)		-1.39 (0.4)	
Difference from metformin	0.44 (-0.16, 1.05)			
Source: FDA Statistical Review				
	Naive	Previously Treated	Naive	Previously Treated
Baseline		8.7	8.2	9.0
Change from baseline (adjusted)		0.2	-1.2	-0.2
Difference from metformin				

Source: FDA Medical and Statistical Review for glimepiride

Glimepiride: Comparison with Adults

		Glimepiride	Metformin	Placebo
Adolescents	Adolescents Naïve Subgroup (ITT)			
	Baseline	8.3	8.2	
	Change from baseline (adjusted)	-1.0	-1.2	
	Difference from metformin	0.20 (-0.30, 0.70)		
Adults	Adult Monotherapy Trial for Naïve Patients (ITT)†			
	Baseline	9.3		9.1
	Change from baseline (adjusted)	-2.2		-1.1
	Difference from placebo		-1.1 (-1.5, -0.8)	

Baseline in Adolescent studies is lower than the adult studies.

† Information obtained from label.

Source: FDA Medical and Statistical Review for glimepiride

Glimepiride: Review

- Sample size is not sufficient to detect non-inferiority with at least 80% power. A NI margin of 0.3 and SD of 1.2 requires 256ptx/arm to achieve 80% power. SD in study is ~2.0, so power is only 40%.
- While there is a 2Wk “stabilization” period, patients on antidiabetics could be randomized with or without washout; non-naïve patients were included and were not washed-out to re-establish baseline HbA1c
- Dose titration for glimepiride was not based on efficacy and gastrointestinal discomfort for metformin limiting the number of patients at the highest dose.
- Some patients are taking anti-diabetic medications while on study drug

Glyburide/Metformin: Design

- Study: 26-Wk superiority study of fixed combination glyburide/metformin vs metformin monotherapy and glyburide monotherapy in 167 children 9-16 yrs old
- Major Inclusion: Drug naïve patients 6.4<HbA1c <14.0 at screening and MFG<350 mg/dl at randomization; Non-naïve patients 6.4<HbA1c <9.0 with 2-4 wk washout and randomized if MFG~200-350 mg/dl
- Treatment: metformin/glyburide 250/1.25mg; metformin 500 mg; glyburide 1.25 mg. Dose titrated at 2,4,6,10,14 wks if MFG>126 mg/dl
- 1^{o} Endpoint: CFB HbA1c to Wk 26

Glyburide/Metformin: Result

	Glyburide/Metformin N=57	Metformin N=54	Glyburide N=49
Mean dose	623/3.1 mg	1500 mg	6.5 mg
Baseline Mean (SD)	7.85 (1.74)	7.99 (1.59)	7.70 (1.69)
Week 26/ Last mean (SD)	7.05 (1.88)	7.46 (1.98)	6.80 (1.40)
Adjusted Mean Change from baseline	-0.80 (0.19)	-0.48 (0.20)	-0.96 (0.21)

Sample size is not sufficient to detect superiority of glucovance over metformin based on effect observed in adults.

	Glyburide/Metformin		Metformin		Glyburide	
Naïve	32	-1.35 (2.00)	25	-0.92 (1.28)	25	-1.12 (1.71)
Non-naive	25	-0.09 (1.63)	29	-0.20 (1.26)	24	-0.68 (1.29)

Source: FDA Medical and Statistical Review for glyburide

Glyburide/Metformin: Comparison with Adults

It is likely that Glucovance would have been effective in pediatric patients with moderately severe hyperglycemia

Adolescents

Baseline HbA1c	Glyburide/Metformin		Metformin		Glyburide	
HbA1c < 7.0	20	-0.09 (0.19)	17	-0.44 (0.14)	22	-0.40 (0.11)
7.0 ≤ HbA1c < 8.0	16	-0.63 (0.39)	15	-0.48 (0.26)	12	-0.53 (0.37)
HbA1c ≥ 8.0	21	-1.60 (0.51)	22	-0.65 (0.39)	15	-1.93 (0.55)

Adults

Baseline HbA1c	Glyburide/Metformin		Metformin		Glyburide	
HbA1c < 8.0	71	-0.90	68	-0.73	77	-0.93
8.0 ≤ HbA1c < 9.0	35	-1.31	39	-1.26	34	-1.27
9.0 ≤ HbA1c < 10.0	30	-2.40	23	-1.50	22	-1.89
10.0 ≤ HbA1c	13	-3.21	11	-1.28	9	-1.87

Source: FDA Medical and Statistical Reviews for glyburide

Rosiglitazone: Design

- Study: 24-Wk non-inferiority study of 2mg bid rosiglitazone (101) to 500 bid metformin (99) in patients 8-17 yrs old. After 4 week placebo run-in, patients are randomized (1:1).
  - NI margin is 0.4.
- Inclusion: $6.5 \leq HbA1c \leq 10$ who had not been treated pharmacologically for T2DM; second inclusion subsequently removed
- Treatment: Dose is doubled after 8 weeks if FPG ≥ 126 mg/dl
- 1^{o} Endpoint: CFB HbA1c to Wk 24

Rosiglitazone: Results

Adolescents

	All Randomized		Naïve	
	Rosiglitazone N=97	Metformin N=98	Rosiglitazone N=55	Metformin N=50
Baseline	7.9 (1.5)	8.2 (1.6)	7.8 (1.4)	7.8 (1.6)
Change from baseline (adjusted)	-0.14 (1.52)	-0.49 (1.65)	-0.32 (1.64)	-0.60 (1.59)
	0.28 (-0.16, 0.72)		0.25 (-0.37, 0.87)	

Adults

	All Randomized		Naïve		
	Rosiglitazone N=166	Placebo N=158	Rosiglitazone N=44	Placebo N=45	Study 1
Baseline	9.02 (1.52)	9.04 (1.66)	8.74 (1.47)	8.54 (1.74)	
Change from baseline (adjusted)	-0.28 (1.22)	0.92 (1.21)	-0.83 (0.93)	0.47 (1.14)	
	Rosiglitazone N=186	Placebo N=173	Rosiglitazone N=46	Placebo N=37	Study 2
Baseline	8.87 (1.54)	8.93 (1.52)	8.86 (1.53)	8.40 (1.45)	
Change from baseline (adjusted)	-0.13 (1.42)	0.79 (1.10)	-1.03	0.14	

Source: FDA Medical and Statistical Review for roziglitazone

Rosiglitazone: Review

- Conclusion: “there was insufficient patients in this study to establish whether these observed mean treatment effects were similar or different, ”i.e., **sample size does not provide sufficient power to demonstrate non-inferiority**
- Rosiglitazone treatment responses between adults and children appear similar in terms of HbA1c
- An indirect comparison to placebo could show that rosiglitazone is potentially efficacious

Considerations for Pediatric Trial

- Because feasibility precludes enrolling sufficient number of patients that provides adequate frequentist statistical power, consider designs and analytical tools that are more efficient.
  - Superiority over placebo with no background metformin
  - Use of priors based on adult treatment responses to boost inferential precision
  - Consider real world data from pediatric treatment responses to guide construct of prior information
- Reduce variance:
  - Design features to reduce disease burden usually induces more variability in the response.
  - “Stabilization” or washout period for patients on antidiabetics to re-establish baseline.
  - Dose titration based on efficacy to push more patients at the highest dose.
  - Stratification of naïve and previously treated patients or explore whether drug has differential effect across baseline HbA1c.
- Increase patient retention

Patient and site friendly trials

- Reduce the number of face-to-face visits and fasting visits
- Make the protocol and eCRFs as simple as possible
  - Example: Eliminate 4/7-point SMBG testing and do not collect SMBG data
- Encourage sites to accommodate after school/evening or weekend visits
- Pay the participant/parent appropriately and provide support (background diabetes drugs, transportation, grocery cards, fitness assistance, cell phone for phone visits)
- Know your patient demographics. Look for sites that are located where patients live (consider minority investigators)

Optimization through Bayesian Approach

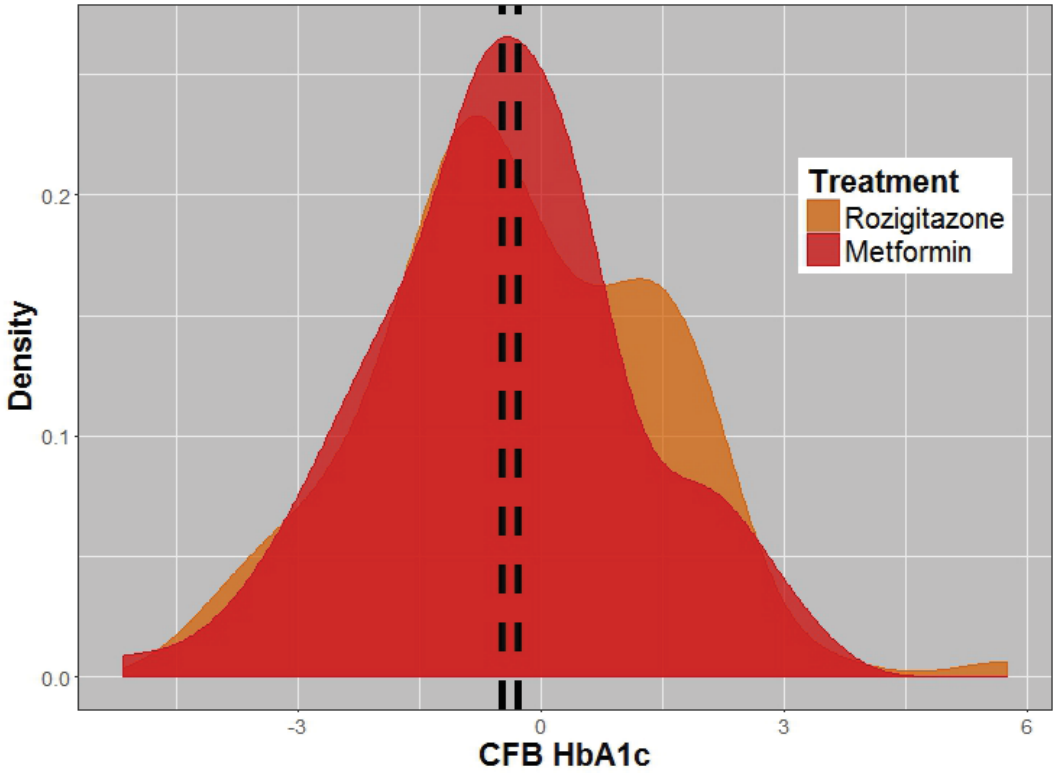
- When is the use of adult data as prior appropriate?
  - ❖Consider similarity in trial element (intervention, lead-ins, etc), populations, etc.
  - ❖See for example, rosiglitazone. The adolescent trial is monotherapy and similar to two adult trials of rosiglitazone.
- What if responses are not similar, are we still able to use informative prior?
  - ❖No. A criteria for similarity can perhaps be created. That criteria should explicitly determine whether the use of the adult prior is warranted.
  - ❖See for example, glimepiride. The change in adults seems to be higher than what was observed in adults.
- Does the placebo rate need to be similar to warrant use as a prior?

Optimizing the Roziglitazone trial: An Illustration

- Available information
  - Adult response on rosiglitazone: 2 monotherapy trials in adults; combined response rate of -0.2112 [-0.3577; -0.0648]
  - Adult response on metformin: Network meta-analysis of metformin monotherapy in adults shows metformin vs TZD treatment estimate is -0.24 [-0.43, -0.05]; direct treatment estimate is 0.05 [-0.63, 0.73][1]
  - Pediatric response on metformin: Meta-analysis on metformin use in children (2 trials)

[1]Palmer, S. C., Mavridis, D., Nicolucci, A., Johnson, D. W., Tonelli, M., Craig, J. C., ... & Natale, P. (2016). Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis. *Jama*, *316*(3), 313-324.

Optimizing the Roziglitazone trial: An Illustration



Generated data (100 patients per arm) from the two treatments almost overlap.

- Requires biological rationale, e.g., similar exposures or response
- **"Validative" approach**: borrowing while checking for consistency

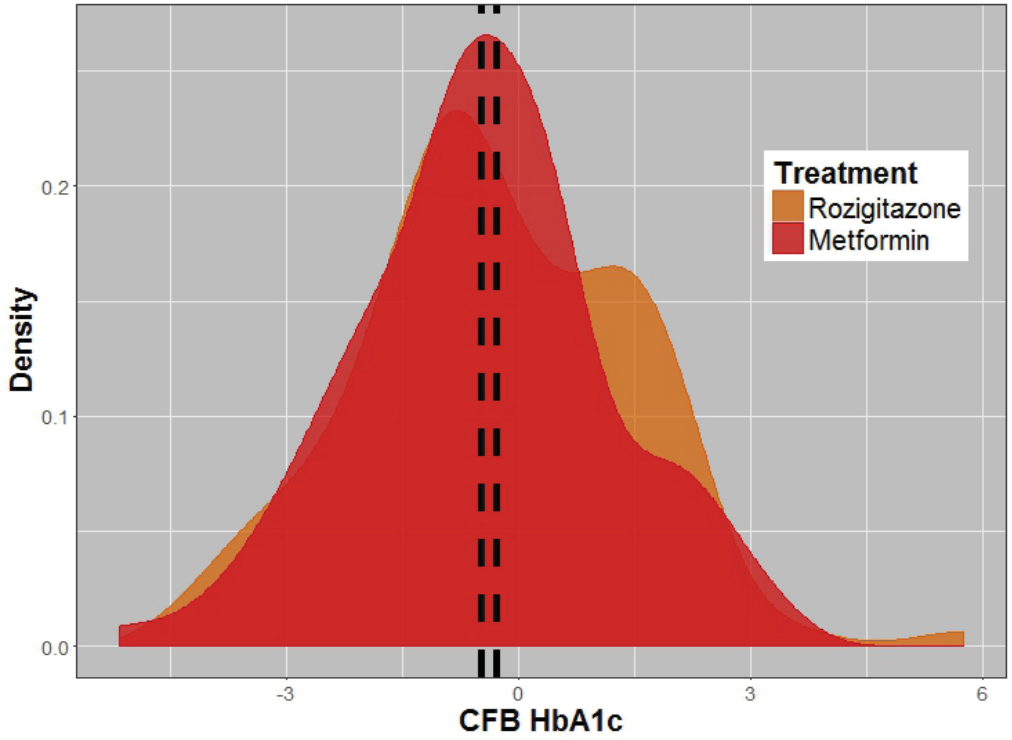
$$\pi'(m_E) = \epsilon\pi(m_E) + (1-\epsilon)\pi(m_E).$$

'Your informative prior'

'Your **I'm-not-so-sure** prior'

- Prior for mean CFB of rosiglitazone: **-0.21 [-0.36; -0.06].**
- Prior for treatment effect of metformin from roziglitazone: **0.05 [-0.63, 0.73]**

Optimizing the Roziglitazone trial: An Illustration



Generated data (100 patients per arm) from the two treatments almost overlap.

Probability of non-inferiority

If not using prior:

P(Metformin-Roziglitazone ≤ -0.3) = **0.680**

If using **robust prior for both rosiglitazone and metformin with 0.25 weight** :

P(Metformin-Roziglitazone ≤ -0.3) = **0.961**

If using **robust prior on metformin only with 0.25 weight**:

P(Metformin-Roziglitazone ≤ -0.3) = **0.970**

If using **robust prior on metformin only with 0.50 weight**:

P(Metformin-Roziglitazone ≤ -0.3) = **0.983**

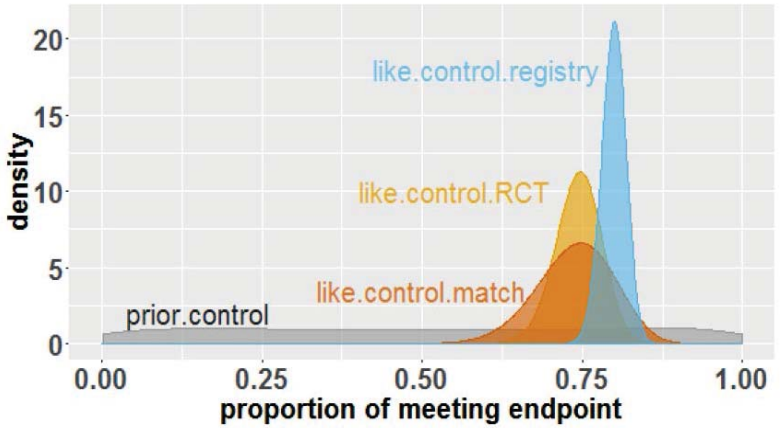
Considerations in Using Results from Adult Trials

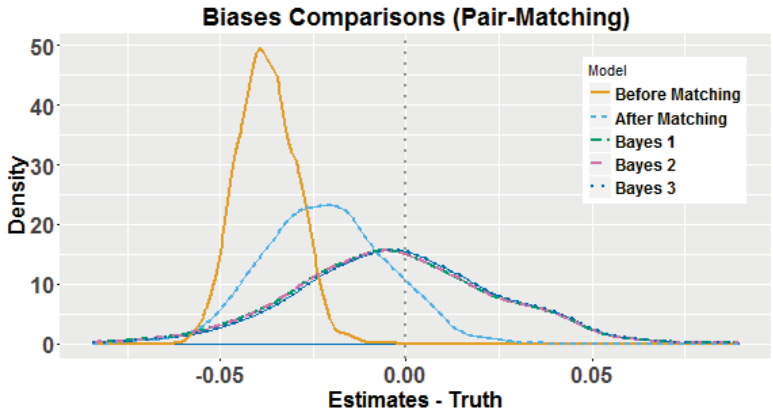
- How to accommodate dose titration?
  - Is it sufficient to have similarity in response regardless of dose titration? Or should distribution of dose be incorporated in the response model?
- Effective sample size of the priors
  - Metformin/TZD is widely used; information from all these trials can be very influential when used as a prior if sample size in the pediatric trial is small.
- Use PK/PD to guide calibration of priors?
  - If sufficient similarity in exposure-response, then more confidence in using adult data (so long as designs are similar)?

Use of RWD: Matching-based prior

Remarks:

- Propensity-based priors are closer to “truth”, i.e., *exchangeability* assumption justified
- Prior is based on baseline characteristics and not on outcome (no cherry- picking!)
- Knowledge of which observations are borrowed
- No more discounting needed
- Prior effective sample size is number of matched samples.





J. Lin, M. Gamalo-Siebers, R. Tiwari. Propensity-based Priors for Bayesian Augmented Controls (Forthcoming)

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