COMPARISON OF DIFFERENT METHODS IN META-ANALYSIS OF SINGLE ARM TRIALS WITH LOW-EVENT RATE BINARY OUTCOME; A CASE STUDY IN CERVICAL CANCER TRIALS

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Background

Meta Analysis of rare events when trials have zero events.

Frequently used methods

- Using normalizing transformation (Arcsine and double arcsine)
- Logit transformation and adding a continuity correction to the trials with zero events
- Exclude trials with zero events. The latter method may introduce bias.
- Literature has shown that transformation such as arcsine has lowest bias with ease of programming in R and Stata.

Alternative approaches.

- Beta Binomial(B-B) approach(GLM with logit link) have substantially smaller bias and mean squared error for rare events with occurrences under five percent, while normal Binomial outperforms B-B for common events.
- simulation approach ; ➡ discrete likelihood approaches perform better than the approximate method . However extensive programming is required.

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Meta analysis of Single proportion(Objective Response Rate) : Observations from the study

- **Data** from 10 **single arm trials** from Systematic literature review on cervical cancer trials including zero events
- Used **transformations** and synthesized the Objective Response rate using preferred methods from literature
- Used **Exact methods** such as Binomial (fixed) and Beta Binomial (random) as event rates were 0% for 4trials .
- **Macros** developed **in SAS 9.4** for all the methods.
- Trials with single arm trials only considered and number of events ranged from 0 to 10 and study size ranged from 16 to 53
- **Differences observed between methods**
- More work need to be done for trials with 2 or more arms and also for trials with higher event rates and large study size.
- Further work using Bayesian methods need to attempted in different scenarios and macros to be developed in SAS

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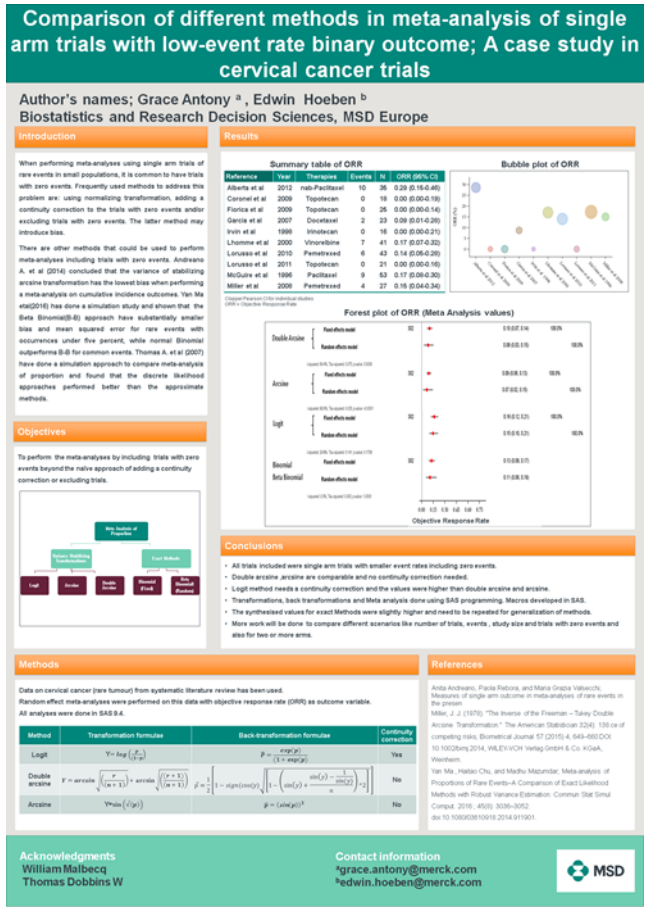

Comparison of different methods in meta-analysis of single arm trials with low-event rate binary outcome; A case study in cervical cancer trials

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Introduction

When performing meta-analyses using single arm trials of rare events in small populations, it is common to have trials with zero events. Frequently used methods to address this problem are: using normalizing transformation, adding a continuity correction to the trials with zero events and/or excluding trials with zero events. The latter method may introduce bias.

There are other methods that could be used to perform meta-analyses including trials with zero events. Andreano A. et al (2014) concluded that the variance of stabilizing arcsine transformation has the lowest bias when performing a meta-analysis on cumulative incidence outcomes. Yan Ma etal(2016) has done a simulation study and shown that the Beta Binomial(B-B) approach have substantially smaller bias and mean squared error for rare events with occurrences under five percent, while normal Binomial outperforms B-B for common events. Thomas A. et al (2007) have done a simulation approach to compare meta-analysis of proportion and found that the discrete likelihood approaches performed better than the approximate methods.

Objectives

To perform the meta-analyses by including trials with zero events beyond the naïve approach of adding a continuity correction or excluding trials.

Results

Summary table of ORR

Reference	Year	Therapies	Events	N	ORR (95% CI)
Alberts et al	2012	nab-Paclitaxel	10	36	0.29 (0.15-0.46)
Coronel et al	2009	Topotecan	0	19	0.00 (0.00-0.19)
Florica et al	2009	Topotecan	0	25	0.00 (0.00-0.14)
Garcia et al	2007	Docetaxel	2	23	0.09 (0.01-0.28)
Irvin et al	1998	Irinotecan	0	16	0.00 (0.00-0.21)
Lhomme et al	2000	Vinorelbine	7	41	0.17 (0.07-0.32)
Lorusso et al	2010	Pemetrexed	6	43	0.14 (0.05-0.28)
Lorusso et al	2011	Topotecan	0	21	0.00 (0.00-0.16)
McGuire et al	1996	Paclitaxel	9	53	0.17 (0.09-0.30)
Miller et al	2009	Pemetrexed	4	27	0.15 (0.04-0.34)

Bubble plot of ORR

Forest plot of ORR (Meta Analysis values)

Objective Response Rate

Conclusions

- All trials included were single arm trials with smaller event rates including zero events.
- Double arcsine ,arcsine are comparable and no continuity correction needed.
- Logit method needs a continuity correction and the values were higher than double arcsine and arcsine.
- Transformations, back transformations and Meta analysis done using SAS programming. Macros developed in SAS.
- The synthesised values for exact Methods were slightly higher and need to be repeated for generalization of methods.
- More work will be done to compare different scenarios like number of trials, events , study size and trials with zero events and also for two or more arms.

Methods

Data on cervical cancer (rare tumour) from systematic literature review has been used.
Random effect meta-analyses were performed on this data with objective response rate (ORR) as outcome variable.
All analyses were done in SAS 9.4.

Method	Transformation formulae	Back-transformation formulae	Continuity correction
Logit	$Y=\log\left(\frac{p}{1-p}\right)$	$\hat{p}=\frac{\exp(y)}{(1+\exp(y))}$	Yes
Double arcsine	$Y=\arcsin\sqrt{\frac{r}{(n+1)}}+\arcsin\sqrt{\frac{(r+1)}{(n+1)}}$	$\hat{p}=\frac{1}{2}\left[1-sign(\cos(y))\sqrt{\left[1-\left(\sin(y)+\frac{\sin(y)-\frac{1}{\pi/2}}{n}\right)^2\right]}\right]$	No
Arcsine	$Y=\sin\left(\sqrt{(p)}\right)$	$\hat{p}=(\sin(y))^2$	No

References

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Thank You
Q&A??

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