The role of overall response rate in planning immuno-oncology biosimilar studies

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Background

- In immuno-oncology biosimilar trials, overall response rate (ORR) is often used as the primary endpoint to access clinical similarity between a biosimilar and its reference product.
- The choice of an equivalence margin (EQM) for ORR defined in absolute rate difference (RD) or relative difference, i.e., rate ratio (RR) is controversial. Consequently, it is not uncommon to specify EQM using both metrics in the same trial.
- A critical misunderstanding is that an EQM in one metric can be equivalently converted to an EQM in another metric with expectation of yielding the same conclusion for both EQMs in the same trial.

Objective

- Provide clarification and correct interpretation of EQM defined using RD vs RR
- Explore the sensitivity of study power on ORR using the two EQM metrics

RD vs RR

Given a fixed reference ORR, the relationship between RD and RR can be expressed as:

$$\mathrm{RD} = p_t - p_r$$
$$\mathrm{RR} = (RD - p_r)/p_r$$

Where p_t denote the ORR in biosimilar arm, p_r for the reference product arm.

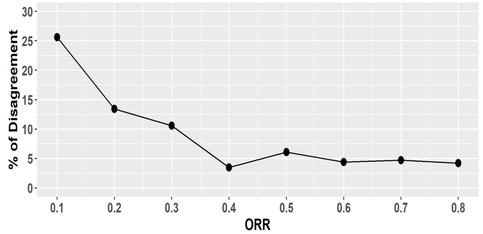
EQM defined in RD vs RR

Assume ORR is the same for both biosimilar and reference products, denoted as p. EQM in RD and RR can be expressed as:

- Assume $[-\delta, \delta]$ in RD, the corresponding EQM in RR is $\left[1-\frac{\delta}{p}, 1+\frac{\delta}{p}\right]$
- Assume $\left[\frac{1}{\lambda}, \lambda\right]$ in RR ($\lambda > 1$), the corresponding EQM in RD is $\left[\left(\frac{1}{\lambda}-1\right)p, (\lambda-1)p\right]$
- Mathematically, RD and RR can be converted for point-estimate or interval. In the concept of EQM, the two metrics cannot be equivalently converted.
- Equivalence established using EQM in one metric does not imply equivalence using the converted EQM in another metric in the same trial.

Simulation 1:

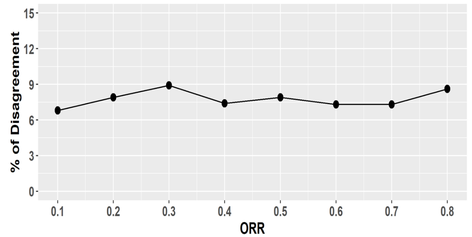
- Reference ORR:10% to 80%; expected difference of ORR: 0%; EQM of [−5%, 5%] in RD, calculate corresponding EQM in RR.
- Sample size is determined with one-sided alpha of 2.5% and power of 80%.
- Run the simulation 1000 times and summarize the percent of time when the conclusions differ using the EQM in RD vs RR.



The disagreement ranges from 4.4% to 25.6%.

Simulation 2:

- Same assumptions as Simulation 1 except that EQM is defined in RR [0.85, 1.15].
- The EQM in RD is calculated for each reference ORR from 10% to 80%.
- Run the simulation 1000 times and summarize the percent of time when the conclusions differ using the EQM in RR vs RD.



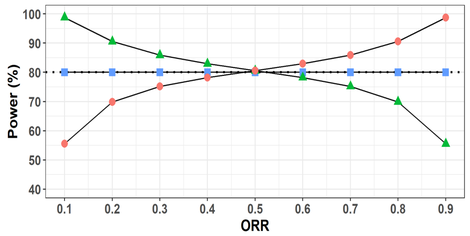
The disagreement ranges from 6.8% to 8.9%.

Sensitivity of Power

To investigate the sensitivity of study power with respect to the change of ORR using EQMs defined in RD and RR, respectively.

Scenario 1:

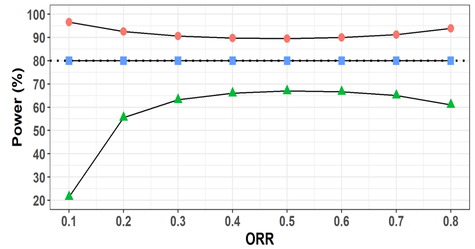
- ORR for the reference:10% to 90%
- Expected difference of ORR: 0%
- EQM in RD: [−5%, 5%]
- Sample size is determined with 80% power and one-sided alpha of 2.5%.
- Re-evaluate study power using estimated sample size above if the ORR is 5% smaller (green) or larger (orange) than its original assumed value.



- The study power changes in opposite directions when ORR>50% vs. <50%
- The study power is more sensitive to ORR if it is closer to 0 or 1 than to 50%

Scenario 2:

- Same as Scenario 1 except that EQM is defined in RR [0.90, 1.11] and ORR ranges from 10% to 80%.



- The study power increases with increasing ORR and vice versa.
- The study power is more sensitive to ORR if it is closer to 0 or 1 than to 50%.
- In general, the ORR has larger impact on study power using EQM in RR than in RD.

Summary

- EQM defined in one metric cannot be equivalently converted to EQM in the another metric.
- Simulations showed that disagreement of conclusion ranged from 4.4% 25.6% and with less impact with EQM in relative difference.
- The impact of ORR change on study power has different implications using different metrics for EQM.
- When designing a trial, it is important to evaluate the sensitivity of power with ORR endpoint as under- or over-estimation of ORR could have opposite impact to the study power using the two EQM metrics.

References:

FDA guidance for Non-Inferiority Clinical Trials to Establish Effectiveness November 2016

EMA Guideline on the choice of the non-inferiority margin July 2005

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Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.

Analyses were performed using R version 4.0.2.