

Underpowered RCTs and external data

- Outline:
 - BBS seminar on external controls (Basel, May 2019): HAs emphasized that underpowered RCTs may sometimes be preferred over single arm studies.
 - Consistent with HA feedback received internally by study teams.
- Questions:
 - Examples of an approval based on such RCT +/- external control?
 - What are circumstances where such a trial can lead to approval?
 - How is the success criteria defined? How to determine sample size?
 - What is the potential role of external data in this context?

Further considerations

It is a challenge to convince cross-functional teams of this approach because

- Teams look for precedence:
 - we have extensive experience in approvals based on single arm studies and
 - lack of examples where underpowered RCTs have been used as labeling-enabling studies.
- Often these single arm studies have no pre-defined success criteria, whereas, for randomized studies it is natural to prospectively assess the precision of the treatment effect estimate.

Is there a role for external controls

- Frequent HA feedback is that external controls are primarily for settings where randomization is not possible. However, in these studies external controls could be used to boost the level of evidence generated in the RCT