

# Decision Schemes for 2-stage designs (TSD) in bioequivalence studies

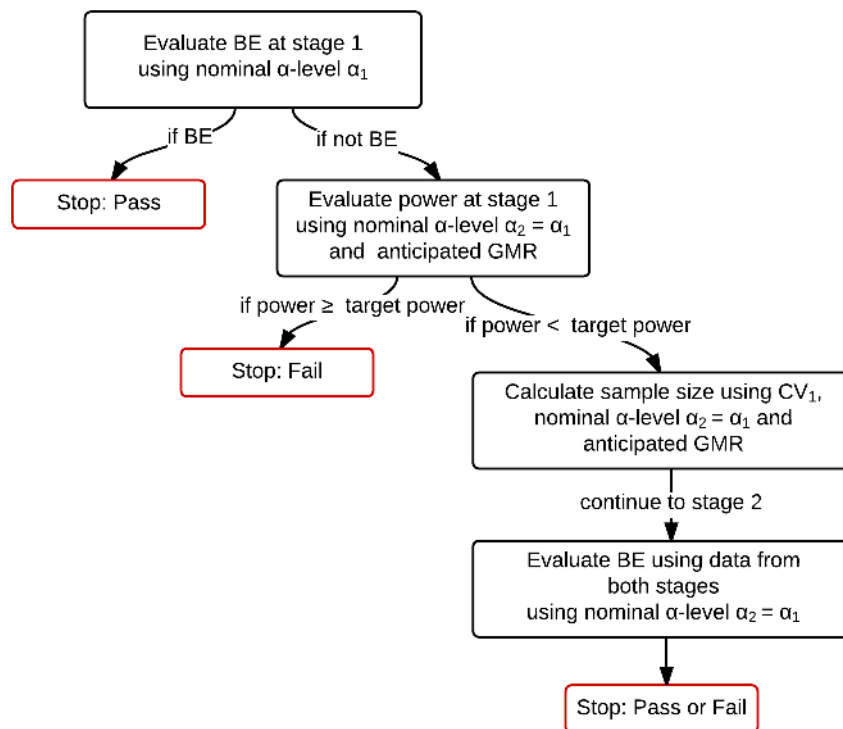
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Version 0.3: Jan 2016

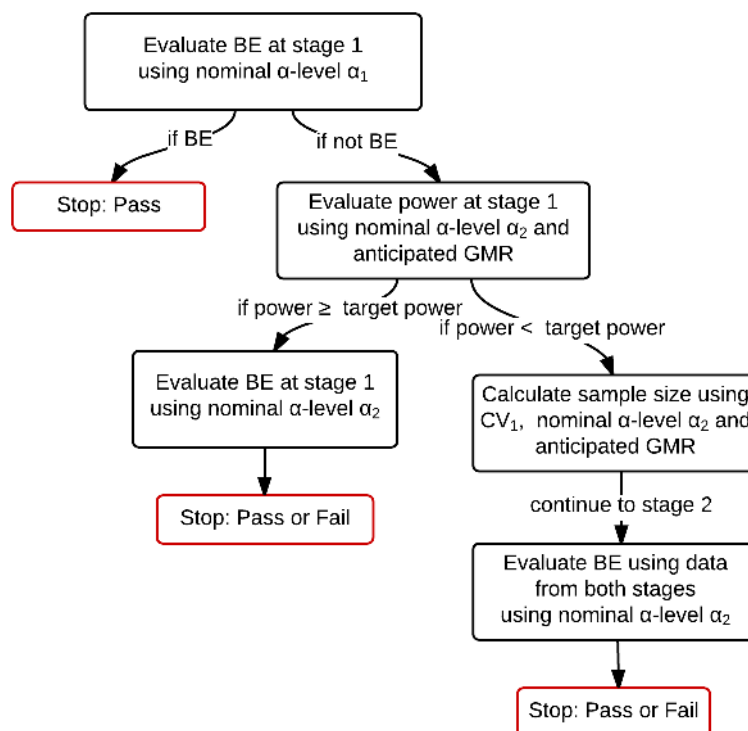
D. Labes

## Type 1 TSD [1] (aka Potvin "Method B"[2])

### Original Potvin Method B with $\alpha_1 = \alpha_2$

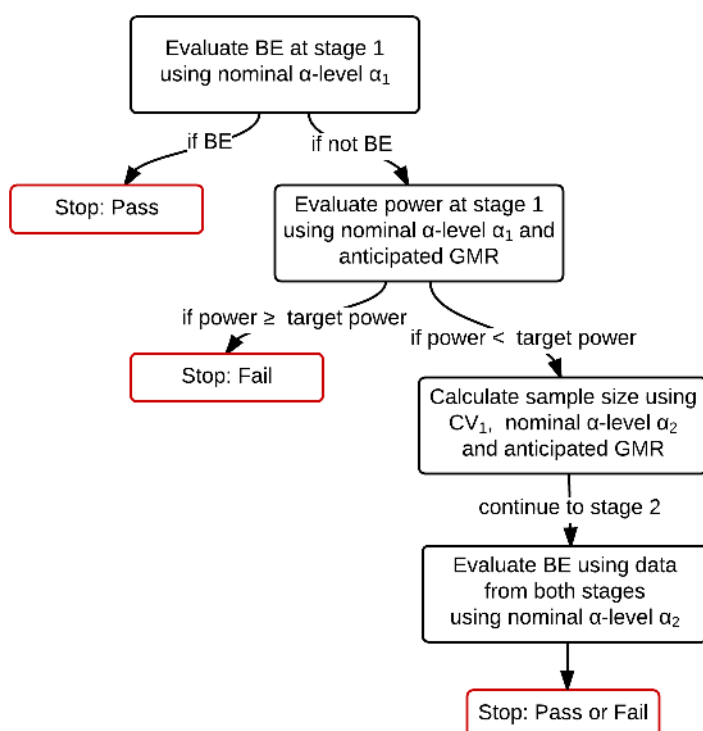


### Method B for arbitrary alphas = Xu et al. "Method E" [8] without futlity check



## Method B for arbitrary alphas as used in so-called MSDBE [3]

(Also used in Power2Stage up to-V0.4-2, now available as `method="B0"`)



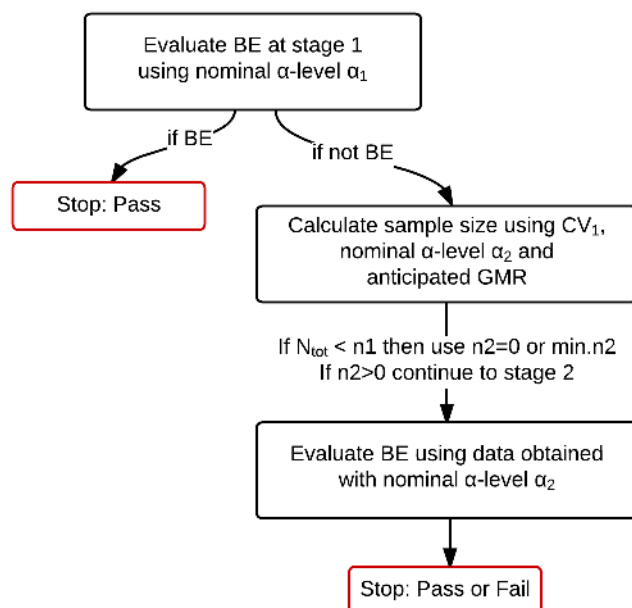
Remark:

In case of 'unsymmetrical'  $\alpha_1$ ,  $\alpha_2$  settings and sufficient high  $n_1$  the reestimated sample size may come out as  $< n_1$  in all the schemes. In that case only the evaluation with stage 2 nominal alpha has to be done. Or alternatively 2 additional subjects recruited for stage 2. The latter option is pure cosmetically since type I error and power are nearly identically.

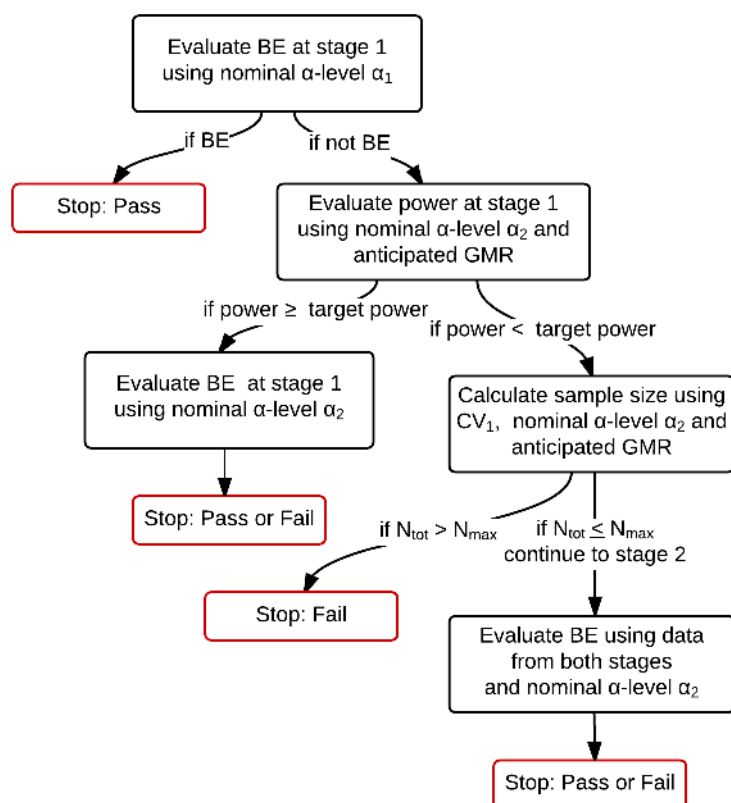
Nominal alpha settings Type 1 TSD:

GMR	Target power	$\alpha_1$	$\alpha_2$	Reference	Max. overall TIE
0.95	0.80	0.0294	0.0294	original Potvin et al. [2]	0.0490
		0.0302	0.0302	Schütz et al. [4]	0.0501
0.90		0.0272	0.0272	Schütz et al. [4]	0.0499
0.95	0.90	0.0284	0.0284	Fuglsang [5]	0.0501
		0.0286	0.0286	Schütz et al. [4]	0.0501
0.90		0.0269	0.0269	Schütz et al. [4]	0.0502
0.95	0.90	0.01	0.04	Zheng et al. [3] 'MSDBE'	NA
0.95/0.90	0.80/0.90	0.001	0.0415	Labes et al. [6]	0.0501 -0.0503

## Method B for arbitrary alphas without power monitoring

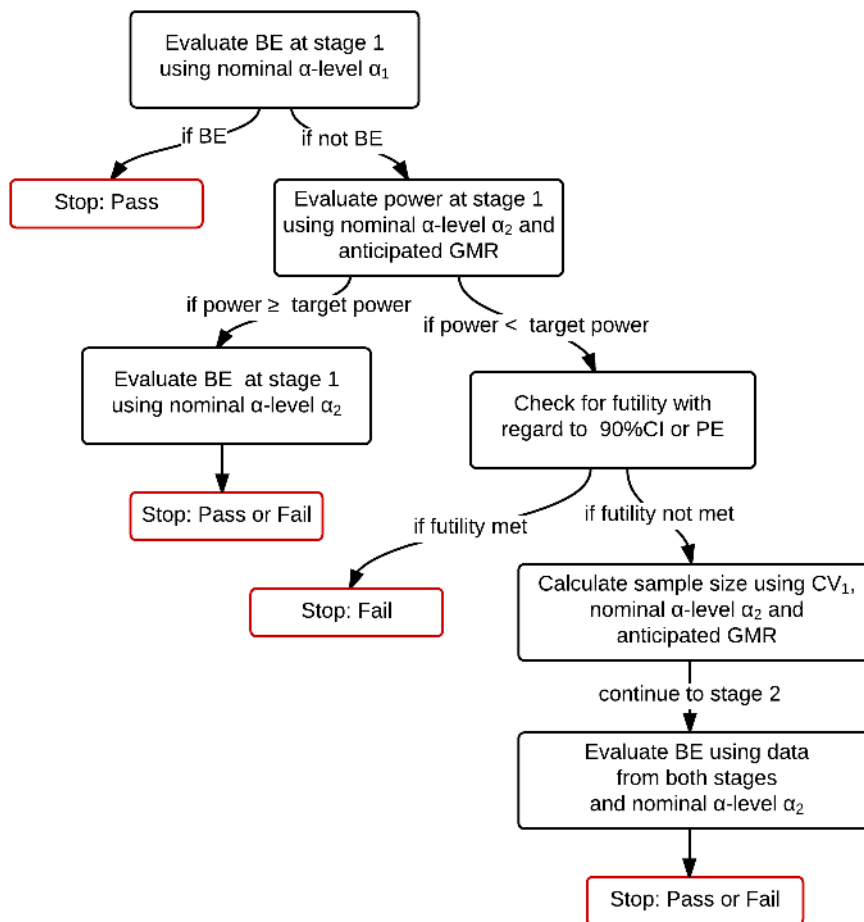


## Type 1 TSD with futility check with regard to a maximum sample size



As Fuglsang [7] has shown power may drop substantially if  $N_{max}$  is chosen too small.

## Type 1 TSD with futility with regard to 90% CI in stage 1 or PE of stage 1



With futility check based on the 90% CI this scheme is "Method E" of Xu et al.[8] if additionally the total sample size is capped with a max.n, i.e. if the estimated sample size came out with a value > max.n then max.n is used.

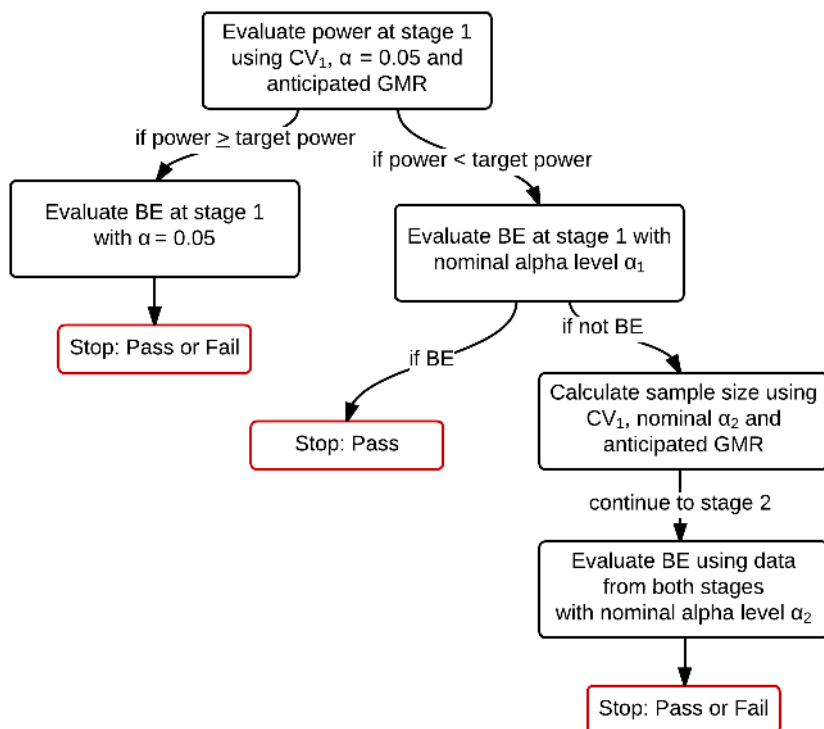
Futility criteria:

- Point estimat (GMR) of stage 1 outside 0.8 ... 1.25 according to Armitage [9], also used in so-called MSDBE [3]
- Point estimat (GMR) of stage 1 outside 0.85 ... 1.17647 according to Bon[10]
- 90% CI outside 0.9 ... 1.1111 (Potvin D, personal communication), see also Xu et al. [8]

Other futility ranges are imaginable.

## Type 2 TSD [1] (aka Potvin "Method C/D" [2], Xu et al. "Method F" [8])

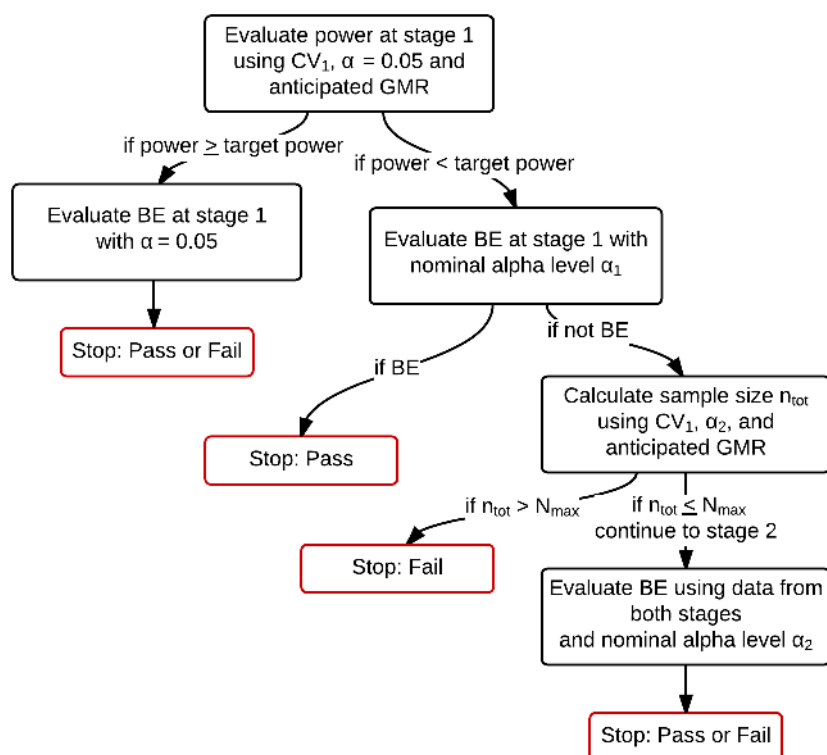
### Original Method C/D with $\alpha_1 = \alpha_2$



Nominal alpha settings for Type 2 TSD:

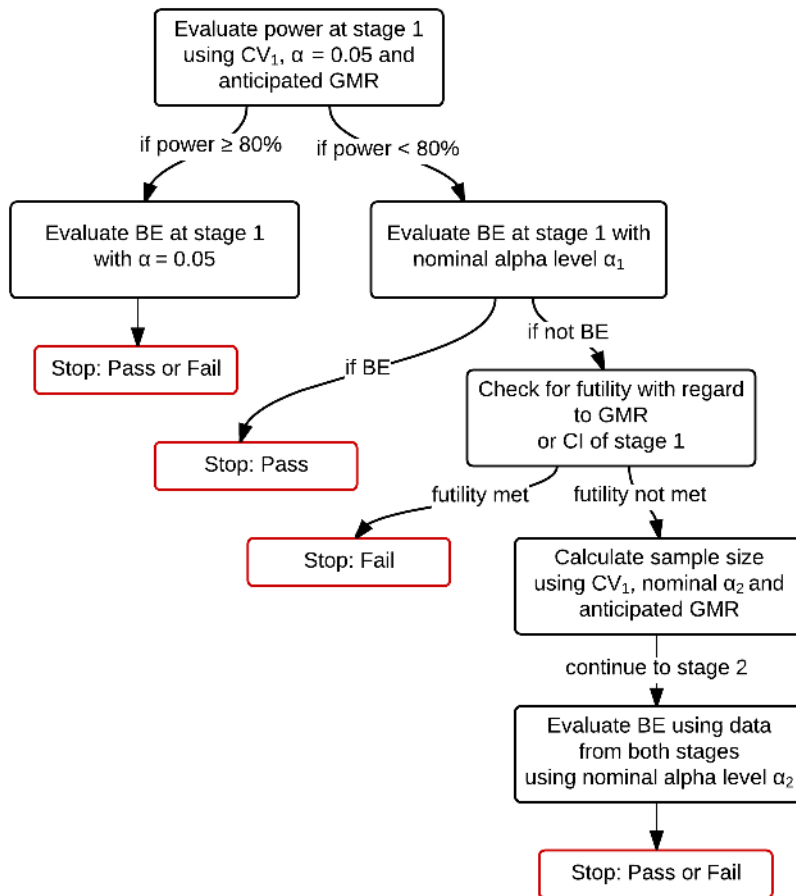
GMR	Target power	$\alpha_1$	$\alpha_2$	Reference	Max. overall TIE
0.95	0.80	0.0294	0.0294	Potvin et al. [2]	<b>0.0514</b>
		0.0282	0.0282	Schütz et al. [4]	0.0501
0.90		0.0280	0.0280	Montague et al. [11]	<b>0.0517</b>
		0.0270	0.0270	Schütz et al. [4]	0.0501
0.95	0.90	0.0274	0.0274	Fuglsang [5]	0.0503
0.90		0.0269	0.0269	Fuglsang [5]	0.0501

## Type 2 TSD with futility stop with regard to a maximum sample size





## Type 2 TSD with futility with regard to the 90% CI of stage 1 or PE of stage 1



Futility criteria w.r.t. GMR or CI from stage 1:

- Point estimate (GMR) of stage 1 outside 0.8 ... 1.25 according to Armitage[9]
- Point estimate (GMR) of stage 1 outside 0.85 ... 1.17647 according to Bon [10]
- 90% CI outside 0.9 ... 1.1111 (Potvin D., personal communication), see also Xu et al. [8]

Other futility ranges are imaginable.

## References

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