Enhancement of Enrichment on the HAP Study Population

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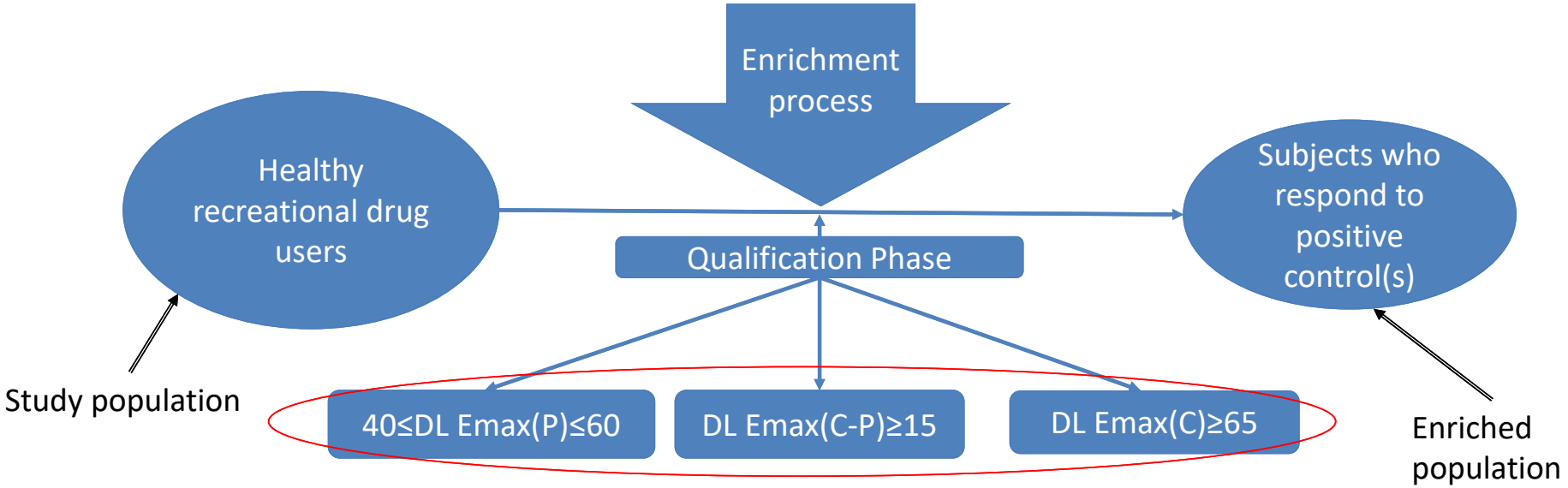
Outline

- Enrichment design used in HAP studies
- Issues in the Treatment Phase
- The Modified Completer Population (MCP) with an example
- Some information from “failed” studies
- Means and standards produced by positive controls based on the proposed MCP
- Remarks

Enrichment Design

- HAP studies have a crossover design. They also have an enrichment design.



The Validation Test

- To validate the study, for Drug Liking (DL)Emax, the test on

$$H_0: \mu_{CH} - \mu_P \leq 15 \quad \text{vs.} \quad H_a: \mu_{CH} - \mu_P > 15$$

  must be statistically significant at 0.05 level.
- Even though subjects who are randomized into the Treatment Phase must have at least 15 points difference in DL Emax scores between positive control(s) and placebo in the Qualification Phase, in the Treatment Phase some subjects could have the difference less than 15. The validation test is to test the mean difference. In other words, the variability in responses from subjects is anticipated and has been taken into consideration.

Issues in the Treatment Phase

- Some completers responded to the positive control with a neutral DL Emax score.
- Some had a negative difference in DL Emax scores between the positive control and placebo.
- Some had similar DL Emax scores to all treatments including placebo.
- Some studies failed the validation test for the comparison between the high dose of positive control (or either positive control when two positive controls used in the study) and placebo for the primary endpoint, and hence resulted in a failed study.
- We heard the voice from the industry that the margin of 15 used in the validation test is too large for some drugs. Some also suggested to delete outliers.

Outliers

- An outlier may be due to variability in the measurement, or it may indicate experimental error; the latter are sometimes excluded from the dataset.
- In HAP studies, crossover design involves observing the same response variate, for example, DL Emax, under different treatment conditions for each subject. Thus, even though we use a univariate model, observations from a subject for each endpoint are multidimensional.
- Commonly used methods to detect multidimensional outliers are Mahalanobis Distance or Jackknife Distance.
- An outlier can cause serious problems in statistical analyses.
- However, outliers should not be simply deleted from analysis datasets.

Modified Completer Population

- In 2019, we recommended using a Modified Completer Population (MCP) as the primary population in HAP studies.
- We proposed two criteria to eliminate completers who are not qualified for the study to ensure that the primary population is improved.

> *In the completer population, eliminate subjects who met any of the following:*
> 1. *Max(all Emax score)-Min(all Emax scores)≤ 5;*
> 2. *Emax(P) > 60 and Emax(P)-Emax(CH)≥5,*
>
> *where CH and P represent high dose of the positive control and placebo, respectively. The Emax refers to the primary endpoint, DL Emax.*

- The observations from eliminated completers for the MCP could be outliers but most of them may not.

Proposed Elimination Criteria for the MCP

In the completer population, eliminate subjects who met any of the following:

1. $Emax(CH) \leq 55$;

(*non-responder to the positive control*)

2. $Emax(P) - Emax(CH) \geq 5$;

(*difference in Emax scores between CH and P is negative*)

3. $Max(all\ Emax\ scores) - Min(all\ Emax\ scores) \leq 5$,

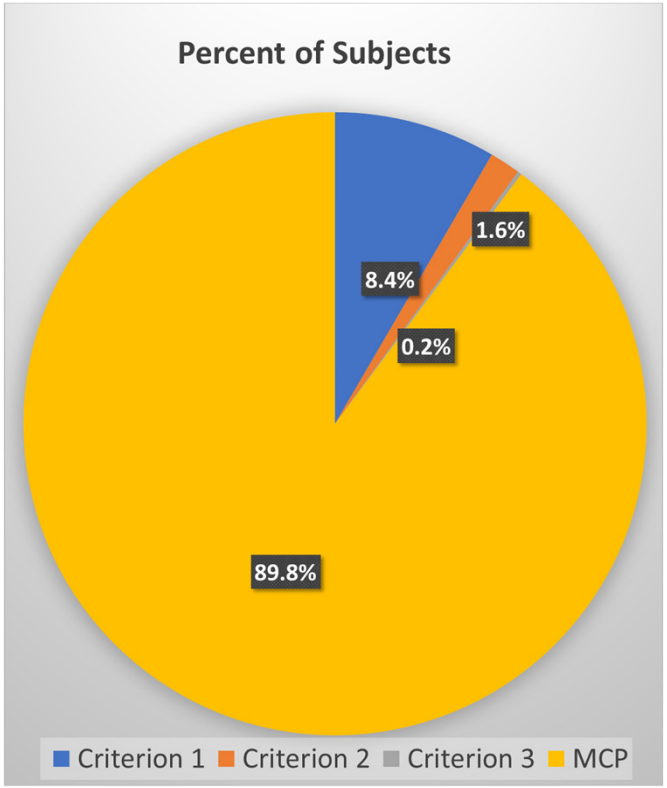
(*Similar Emax scores from a completer across all study treatments including placebo*)

where *CH* and *P* represent high dose of the positive control and placebo, respectively. The Emax refers to the primary endpoint, DL Emax.

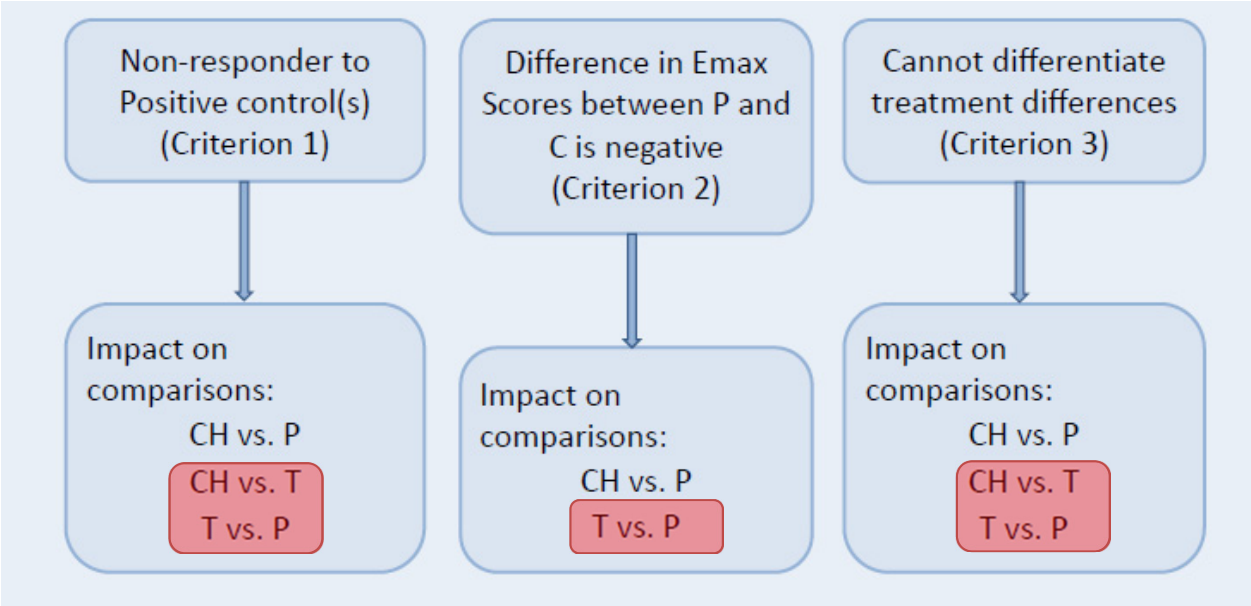
If two positive controls are used in a study, a completer who met any of above criteria for either positive control should be eliminated.

Completers Who Met the Proposed Elimination Criteria in 14 HAP Studies

Study	Route	# of Controls	Criterion 1	Criterion 2	Criterion 3	Total
1	Oral	2	7	0	0	7
2	Oral	1	5	1	0	6
3	Oral	1	6	0	0	6
4	Oral	1	1	0	0	1
5	Oral	1	2	0	0	2
6	Oral	1	0	0	0	0
7	Oral	2	7	2	0	9
8	Oral	2	4	1	0	5
9	IN	1	0	0	0	0
10	IV	1	2	0	0	2
11	Oral	2	5	2	0	7
12	Oral	2	8	3	1	12
13	Oral	1	2	1	0	3
14	Oral	1	2	0	0	2



Impacts of Eliminated Completers on Comparisons



Clearly, these subjects will affect the assessment of the test drug!

An Example

Table 1: DL Emax scores from completers met any of the proposed elimination criteria for MCP in a HAP study

Subject	DL Emax Scores		
	C	T	P
1	50	50	50
2	51	86	51
3	56	51	51
4	50	100	100
5	51	68	62

- Subjects 1, 2, 4 and 5 did not respond to the positive control. The differences between C and P from these subjects vary from 0 to -50.
- The differences between C and T from Subjects 2, 4 and 5 vary from -17 to -50.
- The differences between T and P from subjects 2 and 5 are 6 and 35, respectively.
- Subjects 1 and 3 met criterion 3.
- If we include these subjects in the analyses, the validation test may fail.
- If we keep these subjects in the analyses and reduce the test margin, the validation test may pass. However, we will not be able to properly assess the test drug.

Note: C, T and P denote positive control, test drug and placebo, respectively.

Information from Three "Failed" Studies

Table 2: Comparisons on Means and SDs of DL Emax scores based on CP and the proposed MCP in three "failed" studies

Study	TRT	CP		MCP		Subjects eliminated
		Mean	SD	Mean	SD	
1	CH	68.1	14.6	73.2	12.7	22.90%
	P	53.9	6.3	52.6	3.8	
2	CH	81.6	14.2	82.6	13.3	13.50%
	P	56.2	12.0	55.2	9.9	
3	C1	76.1	17.8	82.7	14.9	28.10%
	C2	78.3	16.0	83.8	13.8	
	P	57.8	16.2	53.3	10.6	

Note: CH and P denote high dose of positive control and placebo, respectively. C1 and C2 denote two positive controls in a HAP study.

Is margin 15 an issue?

Table 3: Means and SDs of DL Emax scores produced by positive controls based on the proposed MCP

Positive control	Mean	SD	Positive control	Mean	SD
Amphetamine 30 mg	81.4	13.7	Ketamine 100 mg	91.3	11.0
Amphetamine 40 mg	82.6	13.3	Lorazepam 6 mg	80.2	11.7
Alprazolam 1.5 mg	83.4	12.7	Phentermine 60 mg	83.0	13.1
Alprazolam 2 mg	83.9	12.7	Suvorexant 40 mg	82.7	14.9
Alprazolam 3 mg	84.7	12.8	Suvorexant 150 mg	83.1	12.6
d-methylphenidate 80 mg	83.0	11.0	Zolpidem 30 mg	83.4	13.7
Diazepam 20 mg	83.6	12.5	Marinol 30 mg	92.2	11.3
Dronabinol 30 mg	88.8	13.4	Methylphenidate 80 mg	73.2	12.7

Impact of using CP or MCP

- Randomization as a method of experimental control has been extensively used in human clinical trials and other biological experiments. It prevents the selection bias and insures against the accidental bias.
- However, a HAP study often has at least 5 treatments crossover. Subjects are randomized to treatment sequences. By using completer population or modified completer population, it may result in incomplete William Square(s), hence, the first-order-carryover effect may not be balanced. The first-order-carryover effect is one of the fixed effects in the mixed effects model. It cannot be dropped out from the model unless the test for the carryover effect is not significant at 0.25 level. If the carryover effect is significant at 0.05 level, only data from first period can be used. In addition, there is a long washout period in HAP studies. Therefore, sequence imbalance has less impact on the statistical analyses.
- In HAP studies subjects are their own control. The elimination of non-completers or unqualified completers will not result bias in treatment comparisons.

Remarks

- We recommend using elimination criteria to establish an MCP and using the MCP as the primary population in HAP studies. This will lead to more reliable comparisons between treatments. MCP elimination criteria should be prespecified and submitted to the Agency for review.
- The sample size determination of a HAP study should use historical data based on an MCP and should take possible elimination of completers into account.
- Using an MCP as the primary population in HAP studies is an enhancement of the enrichment.
- Meanwhile, the investigators should focus on improving the Qualification Phase. If no completer meets any of the elimination criteria, then MCP=CP.

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