Chapter 6

Optimal and Efficient Crossover Designs in One Placebo and Two Active Treatments for Carryover Models

6.1 Introduction

Koch et al. [32] proposed a two period crossover design in ten sequences, for comparison of two active treatments in presence of placebo, so that, treatment and carryover effects are partially orthogonal. This resulted in variance of active treatment contrasts, which remained the same under no carryover, as well as carryover model. Jones and Donev [28] improved their design into three periods design to optimize the active treatment comparison. In one of their designs, treatment effects are orthogonal to carryover effects. However, both the authors have assumed that carryover of both active treatments are equal to γ and that of placebo is $-\gamma$. Also there exist no two treatment two period crossover design which can estimate treatment contrast under self and mixed carryover model (Hedayat and Stufken [21]).

This chapter overcomes both the above limitations and give optimal crossover

designs under, arbitrary carryover of active treatments for four plausible carryover models. Optimal crossover designs for two active treatments and a placebo in two to four periods are given for different number of units. The three and four period crossover designs having two active treatments in presence of placebo estimates treatment contrasts more efficiently under self and mixed carryover model than the two treatments crossover designs. The optimal designs are generated through a computer search algorithm. crossover designs in two to four periods requiring two to twenty units have been constructed and identified for being optimal and efficient under carryover models. Some of these designs are more efficient than those of Hedayat and Stufken [20]. For example, optimal design {3ABA, 3BAB} for $COD(2, 6, 3)$ shown by Hedayat and Stufken [20] under self and mixed carryover model has variance 1 of treatment contrasts, whereas, our design {ABP, BPA, PAB, APB, BAP, PBA} has variance 0.42.

6.2 Models and its estimation

6.2.1 Modified models

The practical situations where purpose of the trial is to compare two new treatments called active treatments with help of a placebo (For example, Trnros and Laurell (a), Trnros and Laurell (b), etc.). Accordingly, all the models considered in this chapter are restricted to three treatments. Model 1.2.1 - 1.2.3 with active treatments A, B and placebo P is referred in this chapter by NCM, TBM and SBM respectively. Again as per assumption that, a placebo has no carryover effect, the traditional model with only treatment A having carryover effect is model 1.2.2, with $\gamma_{d(k-1,j)} = 0$ if $d(k-1, j) = B$

and P. We will refer this model in this chapter as TSM.

Similarly, self and mixed model with only treatment A having carryover effect is model with 1.2.3 $\gamma_{d(k-1,j)} = 0$ if $d(k-1,j) = B$ and P. We will refer this model in this chapter as SSM. These five different fixed effect models, NCM, TSM, TBM, SSM and SBM for continuous response, which cover the different possibilities of the carryover effect. As under SBM, comparison of active treatments, with help of placebo, reduces the variance of treatment contrast. That is, $COD(t+1, n, p)$ performs optimal than $COD(t, n, p)$ under SBM. From Table 6.1, it is clear that, $cod(p)6\{$ABP, BPA, PAB, APB, BAP, PBA$\}$ is optimal and efficient for class $COD(2+1, 6, 3)$, because this design is optimal under SBM and efficient to other models. Note that, class $COD(t+1, n, p)$ contains all the crossover design of $t+1$ and t treatments having subjects n or $n-1$ in p period. Variance of least squares estimator of treatment contrast of shown crossover designs in this chapter, is obtained through computer search algorithm. Idea behind this is to relive the unnecessary restriction which must for to prove optimal design by theoretically. Let us obtain the formula for variances of treatment contrasts in following subsection.

Table 6.1: Optimal and/or Efficient balanced crossover designs for class $COD(2+1, 6, 3)$

Serial no.	Design	n	NCM	TSM	TBM	SSM	SBM
1	AAB,ABA,ABB,BBA,BAB,BAA	6	100	81	81	78	45
2	AAB,2ABB,BBA,2BAA	6	100	99	99	96	25
3	2ABA,ABB,2BAB,BAA	6	100	67	67	62	47
4	ABA,2ABB,BAB,2BAA	6	100	92	92	100	28
5	3ABB,3BAA,3BAA,3ABB	6	100	100	100	-	-
6	ABP,BPA,PAB,APB,BAP,PBA	6	75	63	60	90	100

6.2.2 Variances of treatment contrasts

Variance of treatment contrasts under NCM, TSM, TBM and SSM can be obtained using equations respectively 4.2.8, 4.2.42, 4.2.18 and 4.2.56, by changing concerned information matrix according to two active treatments and one placebo. However, under SBM, normal equations of periods are affected due to $\bar{M}_1'\underline{\gamma}_1 \neq 0$ and $\bar{M}_2'\underline{\gamma}_2 \neq 0$. Hence, normal equations of periods are not free from self carryover effects, as well as mixed carryover effects. Normal equations of subjects, treatments, self carryover and mixed carryover are free from the period effects, but due to above hurdles, all these equations are affected by period effects and needs afresh estimation. In matrix form, Model 1.2.3 is written as,

$$\underline{Y} = \mu\underline{1} + P\underline{\pi} + U\underline{\xi} + T\underline{\tau} + F_1\underline{\gamma}_1 + F_2\underline{\gamma}_2 + \underline{\epsilon}, \tag{6.2.1}$$

Now, by the method of least squares,

$$\begin{bmatrix} \underline{1}'\underline{1} & \underline{1}'P & \underline{1}'U & \underline{1}'T & \underline{1}'F_1 & \underline{1}'F_2 \\ P'\underline{1} & P'P & P'U & P'T & P'F_1 & P'F_2 \\ U'\underline{1} & U'P & U'U & U'T & U'F_1 & U'F_2 \\ T'\underline{1} & T'P & T'U & T'T & T'F_1 & T'F_2 \\ F_1'\underline{1} & F_1'P & F_1'U & F_1'T & F_1'F_1 & F_1'F_2 \\ F_2'\underline{1} & F_2'P & F_2'U & F_2'T & F_2'F_1 & F_2'F_2 \end{bmatrix} \begin{bmatrix} \hat{\mu} \\ \underline{\hat{\pi}} \\ \underline{\hat{\xi}} \\ \underline{\hat{\tau}} \\ \underline{\hat{\gamma}}_1 \\ \underline{\hat{\gamma}}_2 \end{bmatrix} = \begin{bmatrix} \underline{1}'\underline{Y} \\ P'\underline{Y} \\ U'\underline{Y} \\ T'\underline{Y} \\ F_1'\underline{Y} \\ F_2'\underline{Y} \end{bmatrix}$$

$$\Rightarrow \quad \begin{bmatrix} np & n\underline{1}' & p\underline{1}' & r\underline{1}' & \bar{r}_1\underline{1}' & \bar{r}_2\underline{1}' \\ n\underline{1} & nI & J & \frac{n}{t}J & \bar{M}_1' & \bar{M}_2' \\ p\underline{1} & J & pI & N' & \bar{N}_1' & \bar{N}_2' \\ r\underline{1} & \frac{n}{t}J & N & rI & Z_1 & Z_2 \\ \bar{r}_1\underline{1} & \bar{M}_1 & \bar{N}_1 & Z_1' & \bar{r}_1 I & 0 \\ \bar{r}_2\underline{1} & \bar{M}_2 & \bar{N}_2 & Z_2' & 0 & \bar{r}_2 I \end{bmatrix} \begin{bmatrix} \hat{\mu} \\ \underline{\hat{\pi}} \\ \underline{\hat{\xi}} \\ \underline{\hat{\tau}} \\ \underline{\hat{\gamma}}_1 \\ \underline{\hat{\gamma}}_2 \end{bmatrix} = \begin{bmatrix} \underline{1}'\underline{Y} \\ P'\underline{Y} \\ U'\underline{Y} \\ T'\underline{Y} \\ F_1'\underline{Y} \\ F_2'\underline{Y} \end{bmatrix}$$

Normal equations from the above matrix under the assumptions $\underline{1}'\underline{\hat{\pi}} = \underline{1}'\hat{\underline{\xi}} = \underline{1}'\underline{\hat{\tau}} = \underline{1}'\underline{\hat{\gamma}}_1 = \underline{1}'\underline{\hat{\gamma}}_2 = 0$ are,

$$np\hat{\mu} = \underline{1}'\underline{Y}, \tag{6.2.2}$$

$$n\hat{\mu}\underline{1} + n\underline{\hat{\pi}} + \bar{M}_1'\underline{\hat{\gamma}}_1 + \bar{M}_2'\underline{\hat{\gamma}}_2 = P'\underline{Y}, \tag{6.2.3}$$

$$p\hat{\mu}\underline{1} + p\hat{\underline{\xi}} + N'\underline{\hat{\tau}} + \bar{N}_1'\underline{\hat{\gamma}}_1 + \bar{N}_2'\underline{\hat{\gamma}}_2 = U'\underline{Y}, \tag{6.2.4}$$

$$r\hat{\mu}\underline{1} + N\hat{\underline{\xi}} + r\underline{\hat{\tau}} + Z_1\underline{\hat{\gamma}}_1 + Z_2\underline{\hat{\gamma}}_2 = T'\underline{Y}, \tag{6.2.5}$$

$$\bar{r}_1\hat{\mu}\underline{1} + \bar{M}_1\underline{\hat{\pi}} + \bar{N}_1\hat{\underline{\xi}} + Z_1'\underline{\hat{\tau}} + \bar{r}_1\underline{\hat{\gamma}}_1 = F_1'\underline{Y}, \tag{6.2.6}$$

$$\bar{r}_2\hat{\mu}\underline{1} + \bar{M}_2\underline{\hat{\pi}} + \bar{N}_2\hat{\underline{\xi}} + Z_2'\underline{\hat{\tau}} + \bar{r}_2\underline{\hat{\gamma}}_2 = F_2'\underline{Y}, \tag{6.2.7}$$

Using equations 6.2.2-6.2.4 in 6.2.5-6.2.7 gives,

$$\left(rI - \frac{1}{p}NN'\right)\hat{\underline{\tau}} + \left(Z_1 - \frac{1}{p}N\bar{N}_1'\right)\hat{\underline{\gamma}}_1 + \left(Z_2 - \frac{1}{p}N\bar{N}_2'\right)\hat{\underline{\gamma}}_2 = \left(T' - \frac{r}{np}\underline{11}' - \frac{1}{p}NU' + \frac{1}{np}N\underline{11}'\right)\underline{Y}.$$

$$\left(Z_1' - \frac{1}{p}\bar{N}_1N'\right)\hat{\underline{\tau}} + \left(\bar{r}_1I - \frac{1}{p}\bar{N}_1\bar{N}_1' - \frac{1}{n}\bar{M}_1\bar{M}_1'\right)\hat{\underline{\gamma}}_1 - \left(\frac{1}{p}\bar{N}_1\bar{N}_2' + \frac{1}{n}\bar{M}_1\bar{M}_2'\right)\hat{\underline{\gamma}}_2 = \left(F_1' - \frac{\bar{r}_1}{np}\underline{11}' - \frac{1}{p}\bar{N}_1U' + \frac{1}{np}\bar{N}_1\underline{11}' + \frac{1}{np}\bar{M}_1\underline{11}' - \frac{1}{n}\bar{M}_1P'\right)\underline{Y}.$$

$$\left(Z_2' - \frac{1}{p}\bar{N}_2N'\right)\hat{\underline{\tau}} - \left(\frac{1}{p}\bar{N}_2\bar{N}_1' + \frac{1}{n}\bar{M}_2\bar{M}_1'\right)\hat{\underline{\gamma}}_1 + \left(\bar{r}_2I - \frac{1}{p}\bar{N}_2\bar{N}_2' - \frac{1}{n}\bar{M}_2\bar{M}_2'\right)\hat{\underline{\gamma}}_2 = \left(F_2' - \frac{\bar{r}_2}{np}\underline{11}' - \frac{1}{p}\bar{N}_2U' + \frac{1}{np}\bar{N}_2\underline{11}' + \frac{1}{np}\bar{M}_2\underline{11}' - \frac{1}{n}\bar{M}_2P'\right)\underline{Y}.$$

denoting respectively as,

$$C\hat{\underline{\tau}} + D\hat{\underline{\gamma}}_1 + E\hat{\underline{\gamma}}_2 = Q_t\underline{Y}. \tag{6.2.8}$$

$$G\hat{\underline{\tau}} + H\hat{\underline{\gamma}}_1 + K\hat{\underline{\gamma}}_2 = Q_{f1}\underline{Y}. \tag{6.2.9}$$

$$L\hat{\underline{\tau}} + O\hat{\underline{\gamma}}_1 + V\hat{\underline{\gamma}}_2 = Q_{f2}\underline{Y}. \tag{6.2.10}$$

Using equation 6.2.10 in 6.2.9 gives,

$$(G - K\bar{V}L)\hat{\underline{\tau}} + (H - K\bar{V}O)\hat{\underline{\gamma}}_1 = (Q_{f1} - K\bar{V}Q_{f2})\underline{Y}.$$

denoting as,

$$G_1\hat{\underline{\tau}} + H_1\hat{\underline{\gamma}}_1 = Q_{f1}^d\underline{Y}. \tag{6.2.11}$$

Using equation 6.2.9 in 6.2.10 gives,

$$(L - O\bar{H}G)\underline{\hat{\tau}} + (V - O\bar{H}K)\underline{\hat{\gamma}}_2 = (Q_{f2} - O\bar{H}Q_{f1})\underline{Y}.$$

denoting as,

$$L_1\underline{\hat{\tau}} + V_1\underline{\hat{\gamma}}_2 = Q^d_{f2}\underline{Y}. \tag{6.2.12}$$

Information matrix for treatment effects is obtained by using 6.2.11 and 6.2.12 in 6.2.8,

$$(C - D\bar{H}_1G_1 - E\bar{V}_1L_1)\underline{\hat{\tau}} = (Q_t - D\bar{H}_1Q^d_{f1} - E\bar{V}_1Q^d_{f2})\underline{Y}.$$

denoting as,

$$C_d\underline{\hat{\tau}} = Q\underline{Y}. \tag{6.2.13}$$

Variance of the treatment contrasts is,

$$V(\underline{\ell}'\underline{\hat{\tau}}) = (\underline{\ell}'\bar{C}_dQ)(\underline{\ell}'\bar{C}_dQ)'\sigma^2. \tag{6.2.14}$$

6.2.3 The 5M Active Algorithm

In this section, we present a computer algorithm for search of optimal and/or efficient crossover designs under the five models, namely, NCM, TSM, TBM, SSM and SBM. The algorithm involves making comparisons of variances of direct effects among crossover designs of a class for the given model. Several computer algorithms have been given in literature (Jones and Donev [28], John et al. [25], Yang and Stufken [55], Satpati et al. [47] etc.) for search of optimal and/or efficient crossover designs.

The most common approach of these algorithms is that, they begin the search procedure with a 'random' design and attempt to improve it until cannot be improved by applying further steps. Our computer search algorithm starts from the first, trivial possibility, proceeds systematically up to the last possibility, and provides globally optimum crossover design by comparing every possible crossover designs of the specified class and model. A broad outline of the 5M active algorithm, which differs only in step (vi) as compared to 5M algorithm is given below.

(i) Set variance $V(m)$ =a high value (say, 99), for all models numbered $m = 1, \ldots, 5$. Set parameters t, p and n.

(ii) Generate all possible treatment sequences of t treatments in p periods.

(iii) Generate a crossover design d by considering n treatment sequences arbitrarily from those obtained in step (ii) including replications of the sequences.

(iv) Perform equal replication check for the generated design, that is, $(np)/t$ occurrence of each treatment. If all the treatments are not equally replicated then return to step (iii).

(v) Perform balanced occurrence check for treatments in each period, that is, n/t occurrence of each treatment in each period. If all the treatments are not equally replicated in each period then return to step (iii).

(vi) Perform pair wise balanced occurrence of active treatments in two successive periods, that is, each ordered pair of mixed, self active treatments and mixed pair of active and placebo are given to constant number of units. If this condition is not satisfied then return to step (iii).

(vii) Under NCM, TSM, TBM, SSM and SBM indexed respectively $m = 1, 2, \ldots, 5$.

(a) Perform connectedness check for the design d, that is, calculate the rank of the design information matrix (C_d) under model m. If it is not connected, that is, rank of C_d is less than $t-1$, then skip next step and consider next model.

(b) Perform least variance check, that is, compute variances of the least squares estimator of treatment contrasts $V(d, m)$ under model m. If ($V(d, m) >= 0$ & $V(d, m) < V(m)$) then store $V(m) = V(d, m)$ and $optimaldesign(m) = d$.

(viii) Finally, store the design with variance $V(d, m)$ and ranks of the design matrix under NCM, TSM, TBM, SSM and SBM, provided, the design is connected in all five models.

(ix) Repeat (iii) to (viii) for all possible combinations of n treatment sequences.

This algorithm produces optimal crossover designs under each model along with their variances and ranks. All this is stored in a spreadsheet for a glance view of design statistics for optimal and/or efficient crossover designs under given model. Note that optimal crossover design under NCM, TSM, TBM, SSM and SBM is stored respectively as the last five designs in the spreadsheet.

Working of Algorithm

Consider an experimental situation where $t = 3$, $p = 3$, $n = 3$. Let the two active treatments are denoted by 1, 2 and placebo denoted by 3. Step (i) set $V(m) = 99$, $m = 1, 2, \ldots, 5$. Step (ii) generate all the possible sequences. Step (iii) generates

a design say, {111, 111, 111}. As per step (iv), treatment 2 is not equally replicated as treatment 1 and 3, and hence, the algorithm returns to step (iii) and generates second design say, {111, 111, 112}. Again the algorithm shall return to step (iii) and generates designs, say, {111, 111, 113}, {111, 111, 121}, ..., {111, 222, 333}. Now algorithm moves to step (v), all the treatments are equally replicated in each period and hence, algorithm moves to step (vi) but the treatments are not balanced in terms of carryover and hence, algorithm returns to step(iii) and generates the other design {111, 223, 223}, ..., {121, 232, 313}. Now this design satisfies the condition of steps (iv)-(vi). Hence, in step (viia), rank of C_d under NCM is calculated. Here rank of the design matrix is two, that is, design is connected. In step (viib) variances of the least squares estimator of treatment contrasts under NCM is calculated. Also variances of the least squares estimator of treatment contrasts is less than the set variance V(1). Hence, the algorithm stores design {121, 232, 313} as optimal design along with its variance for treatment comparison. Similarly, the algorithm calculates C_d and variances of the least squares estimator of treatment contrasts under TSM, TBM, SSM and SBM one by one according to step (vii). Under all the other four models, the design is connected and hence algorithm stores design {121, 232, 313} as optimal design along with its variance under TSM, TBM, SSM and SBM. Also this design is connected in all five models, algorithm stores this design as design number 1 with its variance and rank. According to step (ix), the algorithm returns to step (iii) and generates other designs. Similarly, the algorithm repeatedly works for other sequence combinations. Since, all fail to yield smaller variance of treatment contrast under TSM and SSM except the design {131, 212, 323}, hence this design is stored as optimal. Also this design is connected in all five models. Hence this design is stored

as design number 2 with its variance and rank. Finally the algorithm generates the following spreadsheet having three sheets named as variance, rank and design.

	Variance under				
Serial	NCM	TSM	TBM	SSM	SBM
1	1	3.083333	3.256198	3.083333	3.256198
2	1	2.333333	3.256198	2.333333	3.256198
3	1	3.083333	3.256198	3.083333	3.256198
4	1	2.333333	3.256198	2.333333	3.256198
5	1	3.083333	3.256198	3.083333	3.256198
6	1	2.333333	3.256198	2.333333	3.256198
7	1	3.083333	3.256198	3.083333	3.256198

	Rank under				
Serial	NCM	TSM	TBM	SSM	SBM
1	2	2	2	2	2
2	2	2	2	2	2
3	2	2	2	2	2
4	2	2	2	2	2
5	2	2	2	2	2
6	2	2	2	2	2
7	2	2	2	2	2

Crossover Designs											
	Subjects				Subjects				Subjects		
Serial	1	2	3	Serial	1	2	3	Serial	1	2	3
1	1	2	3	4	1	2	3	7	1	2	3
	2	3	1		3	1	2		2	3	1
	1	2	3		1	2	3		1	2	3
2	1	2	3	5	1	2	3				
	3	1	2		2	3	1				
	1	2	3		1	2	3				
3	1	2	3	6	1	2	3				
	2	3	1		3	1	2				
	1	2	3		1	2	3				

Here, variance sheet shows that design number 3 to 7 are optimal under NCM, TSM, TBM, SSM and SBM respectively. Design 1 and 2 are designs connected in all the five models. This designs may or may not be optimal under any model. Using the 5M active algorithm, balanced crossover designs for two active treatments and a placebo in two, three and four periods for different number of units are generated. Let us discuss these crossover designs in comparison of two treatment crossover designs. It follows in three sections as crossover designs in two, three and four periods respectively. Also to suit the experimenters about the choice of model, every section has the subsections as, optimal crossover designs for the each specified model, and efficient crossover designs for all the defined models. When experimenter is sure about the type of model, he should prefer selecting optimal design for his model. Otherwise, he should opt for design that is efficient under all possible models. The evaluation

is done for three popularly used models and their practical modifications, namely, NCM, TSM, TBM, SSM and SBM as defined above. Further, crossover designs in ten subjects are compared with those of Koch et al. [32] and Jones and Donev [28] in terms of efficiency, under newly set assumptions. It shows that, our design will be suitable under situations where the assumption of fixed and equal carryover is violated, and the use of unequal replication of treatments is unsuitable.

6.3 Two active treatments and one placebo in two period crossover designs

Recall that in the class of two treatment two period crossover designs, only a few deigns are available which can estimate treatment contrasts unbeatably. Considering crossover deigns in two active treatments and one placebo, increases the availability of such designs. This is because the resultant design is a collection of replicates from the nine possible sequences, AA, AB, AP, BA, BB, BP, PA, PB, PP. Before defining such crossover design, let us consider a practical situation discussed by Senn [50], where such types of crossover designs are used.

Example 6.3.1. This concerns a double-blind placebo controlled crossover trial, designed to measure the onset of action of two doses of formoterol solution aerosol: 12 μg and 24 μg. For practical reasons, it was decided that the patients could only be studied during four visits. Since each treatment day was to be preceded by a general medical evaluation, this meant that only two treatment days were possible. Blindness was maintained using dummy loading, and each patient used two aerosols at each of visits 2 and 4, taking one puff from each. The aerosols were matched and depending

on whether both aerosols were formoterol solution 12 μg, both placebo or one of each, the patient received 24, 0 or 12 μg formoterol. The wash-out period between visits 2 and 3 was approximately one week.

For the above crossover trial, any of the following two period crossover designs is useful, according to the availability of the subjects and possibility of the carryover model. Naturally, an experimenter would prefer a design which is optimal under the most speculated carryover models and simultaneously efficient under the possible models. As per the following Table 6.2, the suitable design could be a two treatment design or a two treatment –one placebo design. Therefore, both types of designs are evaluated and tabulated as belonging to common classes. A class is determined by the number of subjects needed by an experiment. Note that, sometimes two treatment designs are economical and efficient over two treatment –one placebo designs and vice-versa. Thus, an experimenter has the choice to reduce the cost of trial by an amount incurred by one or two subjects, or not. Here, we evaluated and compared crossover designs having subjects in multiples of three (Table 6.2 shows number of subjects from 6 to 21).

6.3.1 Optimal crossover designs under NCM, TSM and TBM

Since the crossover designs in two active treatments and one placebo will allocate the active treatments to less number of subjects than the corresponding two (active) treatment designs, the latter design will have smaller variance for treatment contrasts under NCM, TSM and TBM. Thus, the optimal designs discussed in the Chapter 4 are optimal under NCM, TSM and TBM but are unable to estimate treatment contrast under SBM. Moreover, crossover design in two treatments is not possible in

odd number of subjects. For example, for the class $COD(2, 9, 2)$, no two treatment design is possible but $COD(2+1, 9, 2)$ exists. However, when the experimenter is sure about his model to be NCM, TSM or TBM, then it is better to use $COD(2, 8, 2)$ than $COD(2+1, 9, 2)$. Similarly, for the class $COD(2+1, 15, 2)$, optimal crossover design under NCM is *cod*(p)28{7AB, 7BA} and under TSM and TBM is *cod*(p)29{3AA, 4AB, 4BA, 3BB}. For the class $COD(2+1, 21, 2)$, optimal crossover design under NCM is *cod*(p)48{10AB, 10BA} and under TSM and TBM is *cod*(p)44{5AA, 5AB, 5BA, 5BB}.

Table 6.2: Optimal and/or Efficient balanced crossover designs for classes $COD(2+1, 6, 2)$ to $COD(2+1, 21, 2)$

Serial no.	Design	n	NCM	TSM	TBM	SSM	SBM
7	3AB,3BA	6	100	-	-	-	-
8	2AA,AB,BA,2BB	6	33	100	100	72	-
9	AA,2AB,2BA,BB	6	67	100	100	72	-
10	AB,AP,BA,BP,PA,PB	6	50	69	56	100	100
11	3AA,AB,BA,3BB	8	25	75	75	63	-
12	2AA,2AB,2BA,2BB	8	50	100	100	83	-
13	AA,3AB,3BA,BB	8	75	75	75	63	-
14	4AB,4BA	8	100	-	-	-	-
15	AA,AB,AP,BA,BB,BP,PA,PB,PP	9	38	86	75	100	100
16	AA,AB,AP,BA,BB,BP,PA,PB,PP	9	30	71	63	100	100
17	2AA,3AB,3BA,2BB	10	60	100	100	100	-
18	AA,4AB,4BA,BB	10	80	67	67	67	-
19	5AB,5BA	10	100	-	-	-	-
20	3AA,3AB,3BA,3BB	12	50	100	100	81	-
21	2AA,4AB,4BA,2BB	12	67	89	89	72	-
22	AA,5AB,5BA,BB	12	83	56	56	45	-
23	6AB,6BA	12	100	-	-	-	-
24	2AA,AB,AP,BA,2BB,BP,PA,PB,2PP	12	25	69	62	72	50
25	2AB,2AP,2BA,2BP,2PA,2PB	12	50	62	50	100	100

continue...

Table 6.2: Optimal and/or Efficient balanced crossover designs for classes $COD(2+1,6,2)$ to $COD(2+1,21,2)$

Serial no.	Design	n	NCM	TSM	TBM	SSM	SBM
26	2AA,5AB,5BA,2BB	14	71	83	83	65	-
27	AA,6AB,6BA,BB	14	86	50	50	39	-
28	7AB,7BA	14	100	-	-	-	-
29	3AA,4AB,4BA,3BB	14	57	100	100	79	-
30	4AA,3AB,3BA,4BB	14	43	100	100	79	-
31	AA,2AB,2AP,2BA,BB,2BP,2PA,2PB,PP	15	43	82	70	100	100
32	AA,2AB,2AP,2BA,BB,2BP,2PA,2PB,PP	15	38	71	60	100	100
33	3AA,5AB,5BA,3BB	16	63	94	94	86	-
34	2AA,6AB,6BA,2BB	16	75	75	75	69	-
35	AA,7AB,7BA,BB	16	87	44	44	40	-
36	8AB,8BA	16	100	-	-	-	-
37	4AA,4AB,4BA,4BB	16	50	100	100	92	-
38	4AA,5AB,5BA,4BB	18	56	100	100	80	-
39	3AA,6AB,6BA,3BB	18	67	90	90	72	-
40	2AA,7AB,7BA,2BB	18	78	70	70	56	-
41	9AB,9BA	18	100	-	-	-	-
42	2AA,2AB,2AP,2BA,2BB,2BP,2PA,2PB,2PP	18	33	77	68	87	67
43	3AB,3AP,3BA,3BP,3PA,3PB	18	50	62	51	100	100
44	5AA,5AB,5BA,5BB	20	50	100	100	80	-
45	4AA,6AB,6BA,4BB	20	60	96	96	77	-
46	3AA,7AB,7BA,3BB	20	70	84	84	67	-
47	2AA,8AB,8BA,2BB	20	80	64	64	51	-
48	10AB,10BA	20	100	-	-	-	-
49	3AA,2AB,2AP,2BA,3BB,2BP,2PA,2PB,3PP	21	30	77	69	82	67
50	AA,3AB,3AP,3BA,BB,3BP,3PA,3PB,PP	21	45	77	64	100	100

6.3.2 Optimal crossover designs under SSM and SBM

Remember that, there exist no two treatment two period crossover design which can estimate treatment contrast under SBM. Table 6.2 shows optimal crossover design under SSM and SBM for varying number of subjects n. Incidentally, optimal design

under SSM is also optimal under SBM in two period cases.

From study of the Table 6.2, it is clear that, there are two general constructions of optimal crossover designs under SSM and SBM, exist for varying number of subjects n. For the class $COD(t+1, n, p)$, when $n \equiv 0$ $(mod\ 6)$, consider $n/6$ replications of the $cod(p)10\{$AB, AP, BA, BP, PA, PB$\}$ and, when $n \equiv 3$ $(mod\ 6)$, use $(n-3)/6$ replications of $cod(p)10$ along with $\{$AA, BB, PP$\}$. Under SSM and SBM, crossover design in one placebo and two active treatments has lesser variance of treatment contrast, than that of crossover design in two treatments. Just as $cod(p)15\{$AA, AB, AP, BA, BB, BP, PA, PB, PP$\}$ is optimal under SSM and SBM in class $COD(2+1, 9, 2)$, accordingly $cod(p)31\{$AA, 2AB, 2AP, 2BA, BB, 2BP, 2PA, 2PB, PP$\}$ and $cod(p)50\{$AA, 3AB, 3AP, 3BA, BB, 3BP, 3PA, 3PB, PP$\}$ are optimal under SSM and SBM in their respective classes, $COD(2+1, 15, 2)$ and $COD(2+1, 21, 2)$. Also note that, $cod(p)16\{$AA, AB, AP, BA, BB, BP, PA, PB, PP$\}$ is optimal under SSM and SBM in the class $COD(2+1, 10, 2)$. This shows that, it is better to use this design because it also saves experimental resources on one subject. Similarly, $cod(p)32\{$AA, 2AB, 2AP, 2BA, BB, 2BP, 2PA, 2PB, PP$\}$ is more useful in the class $COD(2+1, 16, 2)$, and, $cod(p)50$ is preferable in the class $COD(2+1, 22, 2)$.

6.3.3 Efficient crossover designs under NCM, TSM, TBM and SSM

From study of the Table 6.2, it is clear that, increasing the number of replications of sequences AB, BA in a design increases the efficiency under NCM, but decreases under TSM, TBM and SSM. In contrast, the replications of sequences AA, BB increases the efficiency under TSM, TBM and SSM, and decreases under NCM. On the other

hand, the replications of sequences in placebo, AP, PA, BP, PB and PP, increases efficiency under SSM and SBM, but decreases under NCM, TSM and TBM. So, it is necessary to find combinations of sequences which can efficiently estimate treatment contrast under all the models. Almost all the optimality studies on crossover designs assume equal replications for their sequences. This will obviously prohibit designs in unequal replications of sequences to show up. Only a computer search algorithm can give assurance to search every possible crossover designs which are optimal and/or efficient under specified models. The results of computer search algorithm (5M active algorithm) are shown in Table 6.2. Below we discuss some interesting cases for each class defined in terms of the crucial parameter of execution, the number of subjects. For the class $COD(2+1,6,2)$, the $cod(p)10\{$AB, AP, BA, BP, PA, PB$\}$ is efficient under NCM, TSM and TBM, but optimal under the remaining two models. When 9 subjects are available, generally statistician use replication of design {AA, AB, BA, BB} as $cod(p)12\{$2AA, 2AB, 2BA, 2BB$\}$ in eight subjects but $cod(p)15\{$AA, AB, AP, BA, BB, BP, PA, PB, PP$\}$ is efficient in the class $COD(2+1,9,2)$. However, if experimenter is 100% sure about no possibility of self and mixed carryover model, then $cod(p)13\{$AA, 3AB, 3BA, BB$\}$ is useful. Interestingly- although not surprisingly enough, the same pattern continued to hold further classes in increasing number of subjects. In the class $COD(2,10,2)$, $cod(p)17\{$2AA, 3AB, 3BA, 2BB$\}$ and $cod(p)18\{$AA, 4AB, 4BA, BB$\}$ perform efficient under four NCM, TSM, TBM and SSM. However, $cod(p)16\{$AA, AB, AP, BA, BB, BP, PA, PB, PP$\}$ is more suitable in case of more possibility of carryover, because it estimates treatment contrast under SBM also. Note that, this design uses 9 subjects and hence it has less efficiency under NCM. Further, under all carryover models, $cod(p)16$ is also efficient than crossover

design of Koch et al. [32] (denoted as K) and Jones and Donev [28] (denoted as $J1$ and $J2$), as shown in Table 6.3. Crossover design of Koch et al. [32] is optimal under SSM and SBM, but it has poor efficiency under TBM. Note that, designs of both the authors are not balanced.

Table 6.3: Efficiency of Koch et al. [32] and Jones and Donev [28] crossover design comparable to our crossover design of Table 6.2 for class $COD(2+1, 10, 2)$

Serial no.	Design	n	NCM	TSM	TBM	SSM	SBM
cod(p)16	AA,AB,AP,BA,BB,BP,PA,PB,PP	9	30	71	63	92	86
cod(p)17	2AA,3AB,3BA,2BB	10	60	100	100	92	-
cod(p)18	AA,4AB,4BA,BB	10	80	67	67	61	-
K	3AB,3BA,AP,PA,BP,PB	10	70	54	36	100	100
J1	3AB,3BA,2AP,PA,BP	10	67	20	19	37	53
J2	3AB,3BA,2AP,PP,BP	10	67	38	20	71	55

A general choice of design for the class $COD(2+1, 12, 2)$ is either six replications of crossover design {AB, BA} or three replications of crossover design {AB, BA, AA, BB}. But $cod(p)21${2AA, 4AB, 4BA, 2BB}, $cod(p)22${AA, 5AB, 5BA, BB} and $cod(p)25${2AB, 2AP, 2BA, 2BP, 2PA, 2PB} perform efficient in this case. However $cod(p)25$ is suitable in case of more possibility of self and mixed carryover. Useful designs according to practical suitability in the class $COD(2+1, 15, 2)$ is $cod(p)31${AA, 2AB, 2AP, 2BA, BB, 2BP, 2PA, 2PB, PP}. However, this $cod(p)31$ has poor efficiency under NCM. When 16 subjects are available, then crossover design in 15 subjects should be used because $cod(p)32${AA, 2AB, 2AP, 2BA, BB, 2BP, 2PA, 2PB, PP} is able to estimate treatment contrast in all five models. In class $COD(2, 18, 2)$, $cod(p)43${3AB, 3AP, 3BA, 3BP, 3PA, 3PB} is optimal under SSM and SBM and efficient to other models. Design $cod(p)50${AA, 3AB, 3AP, 3BA, BB, 3BP, 3PA,

3PB, PP} is efficient under all the models for the class $COD(2+1, 21, 2)$. Also, this design has poor efficiency under NCM.

In general, constructions of optimal and efficient crossover designs under SSM and SBM for the class $COD(t+1, n, p)$ is when $n \equiv 0 \ (mod\ 6)$, $n/6$ replications of $cod(p)10$ and, when $n \equiv 3 \ (mod\ 6)$, $(n-3)/6$ replications of $cod(p)10$ along with {AA, BB, PP}.

6.4 Two active treatments and one placebo in three period crossover designs

A crossover design in two active treatments and one placebo having three periods is given by some of these twenty seven treatment sequences AAA, BAA, PAA, ABA, BBA, PBA, APA, BPA, PPA, AAB, BAB, PAB, ABB, BBB, PBB, APB, BPB, PPB, AAP, BAP, PAP, ABP, BBP, PBP, APP, BPP and PPP. Due to increased options compared to two period crossover designs, treatment contrasts are estimable under all models for all classes that is, according to desirable number of subjects. Also now there are more choices for designs. Before defining such a crossover design, let us consider a practical situation reported by Tsoy et al. [53] for a single center data from a multi-center trial, where such types of crossover designs are used.

Example 6.4.1. Values of forced expiratory volume in one second (FEV_1), obtained after an exercise challenge in a three period three treatment double-blind crossover trial, comparing the protective effect of a single dose of an experimental treatment, formoterol solution aerosol (12 mg), to a single dose of a standard therapy, salbutamol suspension aerosol (100 mg), and placebo for patients suffering from exercise-induced

asthma.

For the above crossover trial, any of the following three period crossover designs would be useful according to the availability of the subjects and choice of the carryover model. Naturally an experimenter would prefer a design which is optimal under the most speculated carryover model, and simultaneously efficient under the possible models. As per the following Table 6.4, the suitable design could be a two treatment design or a two treatment –one placebo design. Therefore, both types of designs are evaluated and tabulated as belonging to common classes. A class is determined by the number of subjects needed by an experiment. Note that, two treatment designs are in even number of subjects, and a two treatment –one placebo designs have subjects in multiples of three numbers get closer to the even numbers. Table 6.4 restricts classes of designs up to 20 but more classes can be developed by using the 5M active algorithm.

6.4.1 Optimal crossover designs under NCM, TSM, TBM and SSM

Although crossover designs in two treatments are optimal under the four models, namely, NCM, TSM, TBM and SSM, but they are not available when there are odd number of subjects like 3, 9, 15 and so on. In class $COD(2+1,3,3)$, the crossover design in two treatments $cod(p)53\{\text{ABB, BAA}\}$ has lesser variance of treatment contrasts under three NCM, TSM and TBM than the $cod(p)54\{\text{APA, BAB, PBP}\}$ having two treatments and one placebo. On the contrary, the $cod(p)54$ is optimal over $cod(p)53$ under SSM. In the class $COD(2+1,9,3)$, the crossover design of two treatments in eight subjects $cod(p)65\{\text{4ABB, 4BAA}\}$ is optimal under NCM, TSM and

TBM, whereas $cod(p)63\{$AAB, 3ABB, 3BAA, BBA$\}$ is optimal under SSM. Similarly, in case of 15 subjects, it is better to leave one unit and use $cod(p)86\{$3AAB, 4ABB, 4BAA, 3BBA$\}$ under NCM and SSM, whereas $cod(p)85\{$3AAA, 4ABB, BAA, 3BAB, 3BBA$\}$ under TSM and TBM.

Table 6.4: Optimal and/or Efficient balanced crossover designs for classes $COD(2+1,3,3)$ to $COD(2+1,20,3)$

Serial no.	Design	n	NCM	TSM	TBM	SSM	SBM
51	ABA,BAB	2	100	25	25	78	100
52	AAB,BBA	2	100	75	75	-	-
53	ABB,BAA	2	100	100	100	-	-
54	APA,BAB,PBP	3	75	32	23	100	92
55	AAB,ABA,ABB,BBA,BAB,BAA	6	100	81	81	78	45
56	AAB,2ABB,BBA,2BAA	6	100	99	99	96	25
57	2ABA,ABB,2BAB,BAA	6	100	67	67	62	47
58	ABA,2ABB,BAB,2BAA	6	100	92	92	100	28
59	3ABB,3BAA	6	100	100	100	-	-
60	ABP,BPA,PAB,APB,BAP,PBA	6	75	63	60	90	100
61	2AAB,2ABB,2BAA,2BBA	8	100	97	97	77	41
62	AAB,ABA,2ABB,2BAA,BAB,BBA	8	100	90	90	70	66
63	AAB,3ABB,3BAA,BBA	8	100	99	99	100	29
64	AAA,AAB,ABA,ABB,BAA,BAB,BBA,BBB	8	75	63	63	50	66
65	4ABB,4BAA	8	100	100	100	-	-
66	ABA,ABP,APB,BAP,BPA,BPB,PAB,PAP,PBA	9	75	55	52	64	100
67	2ABB,APB,2BAA,BPA,PAP,PBP,PPP	9	75	75	75	69	78
68	2ABB,APB,BAA,BAP,BPA,PAA,PBP,PPP	9	72	72	71	70	88
69	AAB,ABB,APB,BAA,BBA,BPA,PAP,PBP,PPP	9	75	73	73	70	84
70	ABB,ABP,APB,BAA,BAP,BPA,PAA,PBB,PPP	9	69	68	68	65	98
71	ABA,ABP,APB,BAP,BPA,BPB,PAB,PAP,PBA	9	60	44	42	65	100
72	2ABB,APB,2BAA,BPA,PAP,PBP,PPP	9	60	60	60	70	78
73	2ABB,APB,BAA,BAP,BPA,PAA,PBP,PPP	9	58	58	57	71	88
74	AAB,ABB,APB,BAA,BBA,BPA,PAP,PBP,PPP	9	60	59	58	71	84
75	ABB,ABP,APB,BAA,BAP,BPA,PAA,PBB,PPP	9	55	55	55	66	98
76	AAB,4ABB,4BAA,BBA	10	100	100	100	94	29
77	2AAB,3ABB,3BAA,2BBA	10	100	99	99	100	63
78	AAA,2ABA,2ABB,2BAA,2BAB,BBB	10	80	66	66	66	89

continue...

Table 6.4: Optimal and/or Efficient balanced crossover designs for classes $COD(2+1,3,3)$ to $COD(2+1,20,3)$

Serial no.	Design	n	NCM	TSM	TBM	SSM	SBM
79	2AAB,ABA,3ABB,3BAA,BAB,2BBA	12	100	93	93	92	64
80	2AAB,4ABB,4BAA,2BBA	12	100	99	99	100	27
81	AAB,5ABB,5BAA,BBA	12	100	100	100	90	22
82	3AAB,3ABA,3BAB,3BBA	12	100	50	50	45	68
83	ABB,ABP,2APB,2BAA,BBA,BPA,PAB,PAP,PBP,PPP	12	69	67	66	81	68
84	2ABP,2APB,2BAP,2BPA,2PAB,2PBA	12	75	63	60	94	100
85	3AAA,4ABB,BAA,3BAB,3BBA	14	94	100	100	76	34
86	3AAB,4ABB,4BAA,3BBA	14	100	93	93	100	45
87	2AAA,2AAB,2ABA,ABB,BAA,2BAB,2BBA,2BBB	14	71	51	51	76	56
88	ABB,2ABP,2APB,BAA,2BAP,2BPA,PAA,PAB,PBA,PBB,PPP	15	71	65	64	90	99
89	2ABB,ABP,2APB,2BAA,BAP,2BPA,PAB,PAP,PBA,PBP,PPP	15	75	69	68	93	90
90	2ABB,ABP,2APB,BAA,2BAP,2BPA,PAA,PAB,PBA,PBP,PPP	15	73	67	66	94	94
91	ABA,2ABP,2APB,2BAP,2BPA,BPB,2PAB,PAP,2PBA	15	75	56	53	87	100
92	ABB,2ABP,2APB,BAA,2BAP,2BPA,PAA,PAB,PBA,PBB,PPP	15	63	59	59	57	99
93	2ABB,ABP,2APB,2BAA,BAP,2BPA,PAB,PAP,PBA,PBP,PPP	15	66	63	63	59	90
94	2ABB,ABP,2APB,BAA,2BAP,2BPA,PAA,PAB,PBA,PBP,PPP	15	64	62	61	60	94
95	ABA,2ABP,2APB,2BAP,2BPA,BPB,2PAB,PAP,2PBA	15	66	51	49	56	100
96	2AAA,3ABA,3ABB,BAA,5BAB,2BBA	16	87	92	92	58	56
97	3AAB,5ABB,5BAA,3BBA	16	100	98	98	73	41
98	AAB,ABA,6ABB,6BAA,BAB,BBA	16	100	98	98	63	46
99	8ABB,8BAA	16	100	100	100	-	-
100	3AAA,ABA,4ABB,BAA,4BAB,3BBA	16	81	84	84	100	46
101	3AAA,3AAB,2ABB,3BBB,3BBA,2BAA	16	63	60	60	44	61
102	4AAB,ABA,4ABB,4BAA,BAB,4BBA	18	100	89	86	75	35
103	AAA,2AAB,5ABA,ABB,3BAA,3BAB,3BBB	18	78	100	58	46	34
104	3AAB,6ABA,3BAA,3BAB,3BBB	18	83	51	100	27	31
105	5AAA,4ABB,4BAB,4BBA,BBB	18	67	75	73	100	25
106	2AAA,3AAB,4ABB,4BAA,3BBA,2BBB	18	78	73	70	65	50
107	3ABP,3BPA,3PAB,3APB,3BAP,3PBA	18	75	60	55	76	100
108	2ABA,2ABP,2APB,2BAP,2BPA,2BPB,2PAB,2PAP,2PBA	18	67	47	43	59	77
109	4ABB,2APB,4BAA,2BPA,2PAP,2PBP,2PPP	18	67	64	61	63	60
110	4ABB,2APB,2BAA,2BAP,2BPA,2PAA,2PBP,2PPP	18	64	61	59	64	68
111	2AAB,2ABB,2APB,2BAA,2BBA,2BPA,2PAP,2PBP,2PPP	18	67	62	60	64	64
112	2ABB,2ABP,2APB,2BAA,2BAP,2BPA,2PAA,2PBB,2PPP	18	61	58	56	60	76

continue...

Table 6.4: Optimal and/or Efficient balanced crossover designs for classes $COD(2+1,3,3)$ to $COD(2+1,20,3)$

Serial no.	Design	n	NCM	TSM	TBM	SSM	SBM
113	3ABP,3BPA,3PAB,3APB,3BAP,3PBA	18	68	54	52	59	100
114	2ABA,2ABP,2APB,2BAP,2BPA,2BPB,2PAB,2PAP,2PBA	18	60	42	40	45	77
115	4ABB,2APB,4BAA,2BPA,2PAP,2PBP,2PPP	18	60	57	58	49	60
116	4ABB,2APB,2BAA,2BAP,2BPA,2PAA,2PBP,2PPP	18	58	54	55	50	68
117	2AAB,2ABB,2APB,2BAA,2BBA,2BPA,2PAP,2PBP,2PPP	18	60	55	56	49	64
118	2ABB,2ABP,2APB,2BAA,2BAP,2BPA,2PAA,2PBB,2PPP	18	55	52	53	46	76
119	AAA,4AAB,ABA,4ABB,4BAA,BAB,4BBA,BBB	20	90	79	81	86	35
120	3AAB,3ABA,4ABB,4BAA,3BAB,3BBA	20	100	81	82	59	46
121	3AAB,7ABB,7BAA,3BBA	20	100	94	96	69	36
122	8AAB,2ABA,2BAA,6BBA,2BBB	20	90	100	86	21	25
123	6AAB,3ABA,ABB,4BAA,3BBA,3BBB	20	85	70	100	33	30
124	4AAA,3AAB,3ABB,BAA,2BAB,5BBA,2BBB	20	70	59	60	100	31
125	9ABA,ABB,BAA,9BAB	20	100	37	38	29	89

6.4.2 Optimal crossover designs under SBM

We know that optimal design literature has shown that $\{\frac{n}{2}\text{ABA}, \frac{n}{2}\text{BAB}\}$, i.e., the design in which half of the subjects receive sequence ABA, and the other half receive BAB is optimal under SBM. It is seen in Chapter 4 that this design is optimal only for the class $COD(2,2,3)$ and $COD(2,4,3)$, and not in general for $COD(2,n,3)$ for given n ($n \equiv 0$ $(mod\ 2)$). These designs are suggested for bioequivalence studies in the FDA [11]. More optimal designs under SBM have already been presented in Chapter 4, for number of subjects $n = 6, 8, 10, \ldots, 20$. Table 6.4 shows that when the class is expanded to include the designs having placebo, then the two treatment one placebo designs become optimal over two treatment designs under SBM. For example, variance of treatment contrasts for $cod(p)57$ is 0.8889, while that for $cod(p)60$ is 0.4167 resulted in 53% gain. Also, crossover designs of approved type are not available in

certain classes, in particular when number of subjects required are 9, 15, and so on. Also so far, no general method of construction is known for varying number of subjects. As per 5M active algorithm construction, the class $COD(2+1, 6, 3)$ design replications constructs the classes $COD(2+1, 6r, 3)$. This means, multiple replications of the uniform *cod*(*p*)60{ABP, BPA, PAB, APB, BAP, PBA} remains optimal under SBM. When the availability of subjects is 9 or 15, *cod*(*p*)66{ABA, ABP, APB, BAP, BPA, BPB, PAB, PAP, PBA} and *cod*(*p*)91{ABA, 2ABP, 2APB, 2BAP, 2BPA, BPB, 2PAB, PAP, 2PBA} are optimal under SBM, respectively in the classes $COD(2+1, 9, 3)$ and $COD(2+1, 15, 3)$. Most of the optimal two treatment crossover designs given for SBM, contains occurrences of self treatment sequences AAA and BBB. The above mentioned $COD(2+1, n, 3)$ designs are suitable over $COD(2, n, 3)$, when self treatment sequences are unacceptable for some experiments. Optimal crossover designs of classes $COD(2+1, n, 3)$ are uniform when $n \equiv 0$ $(mod\ 6)$ and approximately uniform when $n \equiv 3$ $(mod\ 6)$. Notice that, the design introduced here, does not exist for number of subjects is 10, 16, 20 and so on, due to lack of balance in periods. In these cases, designs in number of subjects 9, 15, 18 and so on, in general, crossover design less by one or two subjects may be used without loosing optimality. For example, *cod*(*p*)71{ABA, ABP, APB, BAP, BPA, BPB, PAB, PAP, PBA} in 9 subjects is optimal than *cod*(*p*)78{AAA, 2ABA, 2ABB, 2BAA, 2BAB, BBB} in 10 subjects. Similarly, *cod*(*p*)95{ABA, 2ABP, 2APB, 2BAP, 2BPA, BPB, 2PAB, PAP, 2PBA} in 15 subjects is optimal than *cod*(*p*)101{3AAA, 3AAB, 2ABB, 3BBB, 3BBA, 2BAA} in 16 subjects, and, *cod*(*p*)113{3ABP, 3BPA, 3PAB, 3APB, 3BAP, 3PBA} in 18 subjects is optimal than *cod*(*p*)125{9ABA, ABB, BAA, 9BAB} in 20 subjects. Further, *cod*(*p*)71 is optimal under SBM than crossover design of Koch

et al. [32] design (denoted as K) as well as Jones and Donev [28] designs (denoted as $J1$ and $J2$) as shown in Table 6.5. Crossover design $J1$ of Jones and Donev [28] is optimal for the treatment contrast $\tau_A - \tau_B$ and $\tau_A - \tau_P$ but not for the treatment contrast $\tau_B - \tau_P$ as it has efficiency 90% whereas, $cod(p)71$ is optimal for all three treatment contrasts. Note that, designs of both the authors are not balanced.

Table 6.5: Efficiency of Koch et al. [32] and Jones and Donev [28] crossover design comparable to our crossover design of Table 6.2 for class $COD(2 + 1, 10, 3)$

Serial no.	Design	n	NCM	TSM	TBM	SSM	SBM
cod(p)71	ABA,ABP,APB,BAP,BPA,BPB,PAB,PAP,PBA	9	60	44	42	65	100
cod(p)72	2ABB,APB,2BAA,BPA,PAP,PBP,PPP	9	60	60	60	70	78
cod(p)73	2ABB,APB,BAA,BAP,BPA,PAA,PBP,PPP	9	58	58	57	71	88
cod(p)74	AAB,ABB,APB,BAA,BBA,BPA,PAP,PBP,PPP	9	60	59	58	71	84
cod(p)75	ABB,ABP,APB,BAA,BAP,BPA,PAA,PBB,PPP	9	55	55	55	66	98
K	3ABB,3BAA,APP,PAA,BPP,PBB	10	70	70	70	42	46
J1	PAB,BAP,2PBA,3ABP,BPA,2BAB	10	80	49	46	72	100
J2	PAB,BAP,PBA,ABP,BAA,ABB,2ABA,2BAB	10	90	61	59	73	74

6.4.3 Efficient crossover designs under NCM,TSM,TBM,SSM and SBM

Most of the crossover designs in two treatments, have poor efficiency under SBM. Inclusion of a placebo as an additional treatment improves the efficiency of a active treatment comparison considerably. Crossover designs in placebo and two active treatments have additional benefit in analysis as seen in Chapter 5. For example, $cod(p)60$ has least variance for treatment contrasts under SBM. This design is now

optimal under SBM, incidentally it is also efficient under the remaining four models. Hence, in class $COD(2+1,6,3)$, $cod(p)60$ is optimal and efficient than the crossover design {3ABA, 3BAB} of FDA [11], {ABB, ABA, AAB, BAA, BAB, BBA} of Hedayat and Stufken [21] and {2ABA, ABB, 2BAB, BAA} of Chapter 4. In the class $COD(2+1,9,3)$, both $cod(p)68${2ABB, APB, BAA, BAP, BPA, PAA, PBP, PPP} and $cod(p)69${AAB, ABB, APB, BAA, BBA, BPA, PAP, PBP, PPP} are more efficient than $cod(p)66${ABA, ABP, APB, BAP, BPA, BPB, PAB, PAP, PBA}, because both designs have more than 70% efficiency in all five models, while the latter is optimal under SBM, but has only 55% and 52% efficiency under TSM and TBM respectively. In the class of twelve subjects designs, $cod(p)79${2AAB, ABA, 3ABB, 3BAA, BAB, 2BBA} and $cod(p)84${2ABP, 2APB, 2BAP, 2BPA, 2PAB, 2PBA} are efficient under all five models, with former design optimal under NCM and the next under SBM. In the class $COD(2+1,15,3)$, two designs perform well. Specifically speaking, when an experimenter has original interest in ensilability of TSM and TBM then he should use $cod(p)90${2ABB, ABP, 2APB, BAA, 2BAP, 2BPA, PAA, PAB, PBA, PBP, PPP} because it is more efficient than $cod(p)91$ and otherwise, should use $cod(p)91$ because it is optimal under SBM and efficient under the remaining models. In class $COD(2+1,18,3)$, although number of choices of designs are available as replication of smaller designs, but the two designs $cod(p)107${3ABP, 3BPA, 3PAB, 3APB, 3BAP, 3PBA} and $cod(p)111${2AAB, 2ABB, 2APB, 2BAA, 2BBA, 2BPA, 2PAP, 2PBP, 2PPP} give efficient estimation of treatment contrast under all five models. $cod(p)107$ is optimal under SBM, whereas $cod(p)111$ has efficiency more than 60% in all five models. Note that, we can obtain more efficient designs in $COD(2+1,18,3)$

using the 5M active algorithm. The designs listed in Table 6.4 are obtained by replication of smaller designs. This shows that, designs will certainly have more than 50% efficiency under TSM and TBM while being optimal under SBM.

6.5 Two active treatments and one placebo in four period crossover designs

All the possible combinations of three treatments in four periods, have eighty one treatment sequences. Here, we have restricted the number of subjects to be at most nine because, cases of the above crossover designs in higher number of subjects is often unlikely in practice. However, an interesting case of the said crossover design in twelve subjects is considered, because there is opportunity to generate crossover designs which are nearly uniform in subjects. Before discussing about the crossover designs, let us consider as a motivational example, the phase IIa trial $TD-4208$, reported by Theravance, for the treatment of chronic obstructive pulmonary disease (COPD) (https://www.centerwatch.com/clinical-trials/results/new-therapies/nmt-details.aspx?CatID=44).

Example 6.5.1. The randomized, double-blind, four-period crossover study enrolled subjects with moderate to severe COPD. The subjects were randomized to receive TD-4208 (350 mcg and 700 mcg), ipratropium bromide, and placebo, each administered as single doses via a nebulizer for four doses. The primary endpoint of the study was mean change from baseline in peak FEV1 compared to placebo.

In the above situation, one of the following four period crossover designs is useful according to the availability of the subjects and possibility of the carryover model.

Table 6.6: Optimal and/or Efficient balanced crossover designs for classes $COD(2+1,3,4)$ to $COD(2+1,14,4)$

Serial no.	Design	n	NCM	TSM	TBM	SSM	SBM
126	AABA,BBAB	2	75	55	55	24	81
127	AABB,BBAA	2	100	91	91	24	81
128	ABAA,BABB	2	75	55	55	24	81
129	ABAB,BABA	2	100	18	18	26	88
130	ABBA,BAAB	2	100	91	91	24	81
131	ABBA,BPPB,PAAP	3	75	67	68	55	100
132	APPA,BAAB,PBBP	3	75	73	68	41	100
133	AABB,BPPA,PBAP	3	100	100	100	97	61
134	ABBP,BAPB,PPAA	3	80	80	76	100	50
135	AAPP,BPAB,PBBA	3	80	75	72	87	72
136	AABB,2ABBA,2BAAB,BBAA	6	100	100	100	99	34
137	2AABB,ABBA,BAAA,BBAA,BBAB	6	92	92	92	100	34
138	AABB,ABAA,ABBA,BAAB,BABB,BBAA	6	92	90	90	92	35
139	ABBP,APPB,BAAP,BPPA,PABB,PBAA	6	63	63	63	90	76
140	AABB,APBP,BAPP,BBAA,PBPA,PPAB	6	67	67	67	87	76
141	ABPA,APBP,BABA,BPAB,PAPB,PBAP	6	65	55	52	96	97
142	ABAB,APBP,BABA,BPAP,PAPB,PBPA	6	67	54	54	95	100
143	2AABB,2ABBA,2BAAB,2BBAA	8	100	100	100	96	34
144	2AABA,2ABBA,2BAAB,2BBAB	8	88	73	73	73	35
145	AABB,ABBA,APBP,BAAB,BBAA,BPAP,PAPB,PBPA,PPPP	9	75	75	75	94	83
146	ABAB,APBP,APPB,BABA,BBAA,BPAP,PABP,PAPB,PBPA	9	75	70	68	96	99
147	ABBA,ABPB,APBP,BAAP,BABA,BPAP,PAPB,PBPA,PPAB	9	73	67	66	100	100
148	AABB,ABPP,APPB,2BBAA,BPAP,PABP,PAPB,PPBA	9	75	75	75	89	81
149	AABB,ABBA,APBP,BAAB,BBAA,BPAP,PAPB,PBPA,PPPP	9	60	60	60	79	83
150	ABAB,APBP,APPB,BABA,BBAA,BPAP,PABP,PAPB,PBPA	9	60	56	55	81	99
151	ABBA,ABPB,APBP,BAAP,BABA,BPAP,PAPB,PBPA,PPAB	9	59	54	53	84	100
152	AABB,ABPP,APPB,2BBAA,BPAP,PABP,PAPB,PPBA	9	60	60	60	75	81
153	3AABB,2ABBA,2BAAB,3BBAA	10	100	100	100	100	42
154	2AABB,3ABBA,3BAAB,2BBAA	10	100	100	100	100	42
155	3AABB,2ABBA,BAAA,BAAB,2BBAA,BBAB	10	95	95	95	100	42
156	2AABA,ABAB,2ABBA,2BAAB,BABA,2BBAB	10	90	67	67	72	44

continue...

Table 6.6: Optimal and/or Efficient balanced crossover designs for classes $COD(2+1,3,4)$ to $COD(2+1,14,4)$

Serial no.	Design	n	NCM	TSM	TBM	SSM	SBM
157	3AABB,3ABBA,3BAAB,3BBAA	12	100	100	100	100	36
158	3ABAA,3ABBA,3BAAB,3BABB	12	88	73	73	76	38
159	2ABPP,2APBB,2BAPP,2BPAA,2PABB,2PBAA	12	63	63	63	74	80
160	2ABPB,2APBA,2BAPA,2BPAP,2PABP,2PBAB	12	63	53	50	89	100
161	AABP,ABBP,2APPB,BAAP,BBAP,2BPPA,2PABB,2PBAA	12	63	62	62	88	81
162	2ABPP,2APBB,2BAPP,2BPAA,2PABB,2PBAA	12	54	54	54	64	80
163	2ABPB,2APBA,2BAPA,2BPAP,2PABP,2PBAB	12	54	45	43	77	100
164	AABP,ABBP,2APPB,BAAP,BBAP,2BPPA,2PABB,2PBAA	12	54	54	54	76	81
165	3AABB,4ABBA,4BAAB,3BBAA	14	100	100	100	100	42
166	4AABB,3ABBA,BAAA,2BAAB,3BBAA,BBAB	14	96	97	97	100	42
167	AABA,2AABB,ABAA,3ABBA,3BAAB,BABB,2BBAA,BBAB	14	93	90	90	93	44

6.5.1 Optimal crossover designs under NCM, TSM, TBM and SSM

In Chapter 4, optimal crossover designs under NCM, TSM, TBM and SSM were obtained for various even number of subjects. Obviously, it could not include crossover designs having odd number of subjects such as 3, 9, 15 and so on. These designs exist for crossover designs in three treatments. Among these three treatment crossover designs, only for the class $COD(2+1,3,4)$, $cod(p)133\{$AABB, BPPA, PBAP$\}$ is optimal under NCM, TSM and TBM, and, $cod(p)134\{$ABBP, BAPB, PPAA$\}$ is optimal under SSM, however, for the remaining two classes, crossover designs of Chapter 4 remain optimal because they carry more replications of treatments. Comparison of crossover designs in two active treatments with and without help of placebo shown in Table 6.6 clearly shows that, it is better to forgo one unit and use optimal crossover design under NCM, TSM, TBM and SSM given in Chapter 4, for number of subjects

9, 15 and so on.

6.5.2 Optimal crossover designs under SBM

The crossover designs in one placebo and two active treatments have lesser variance of treatment contrasts under SBM, than those of two treatment crossover designs of Hedayat and Stufken [21], Ozan and Stufken [45]. These design is also optimal than the two treatment four period crossover design discussed in Chapter 4. Note that, in class $COD(2+1,3,4)$, two designs $cod(p)131\{$ABBA, BPPB, PAAP$\}$ and $cod(p)132\{$APPA, BAAB, PBBP$\}$ are optimal under SBM. This design also outperform the COD(2,2,4) in variance, making it only efficient under SBM. In the same way, when trial has 6 subjects, $cod(p)142\{$ABAB, APBP, BABA, BPAP, PAPB, PBPA$\}$ is optimal under SBM, and hence preferable over the previous optimal two treatment $cod(p)138\{$AABB, ABAA, ABBA, BAAB, BABB, BBAA$\}$ which has an efficiency of only 35% under SBM. Similarly, $cod(p)147\{$ABBA, ABPB, APBP, BAAP, BABA, BPAP, PAPB, PBPA, PPAB$\}$ is optimal under SBM in class $COD(2+1,9,4)$, with very low variance than the two treatment $cod(p)144\{$2AABA, 2ABBA, 2BAAB, 2BBAB$\}$, which has an efficiency of only 35%. The same discussion can go on for more than nine subjects, but we switch to an interesting case of crossover designs in twelve subjects. When $n = 12$, we consider only those sequences which are approximately uniform in subjects. That is, only those sequences which contain all three treatments at least once. In this class $COD(2+1,12,4)$, the $cod(p)160\{$2ABPB, 2APBA, 2BAPA, 2BPAP, 2PABP, 2PBAB$\}$ is optimal with substantial gain in efficiency, compared to the crossover design in two treatments, the $cod(p)158\{$3ABAA, 3ABBA, 3BAAB, 3BABB$\}$ having efficiency 38%. As regards, trials in ten subjects, the crossover design

in one placebo and two active treatments, given by $cod(p)151$\{ABBA, ABPB, APBP, BAAP, BABA, BPAP, PAPB, PBPA, PPAB\} in nine subjects, beats two treatment $cod(p)153$\{3AABB, 2ABBA, 2BAAB, 3BBAA\}, under SBM. Similarly, $cod(p)163$ is also optimal in class $COD(2+1, 14, 4)$. Hence it is better to use $cod(p)163$ in 12 subjects for estimation of SBM, with savings of cost incurred on two subjects.

6.5.3 Efficient crossover designs under NCM, TSM, TBM, SSM and SBM

For experimenters who want to switch from one to the other models, it is desirable that a crossover design is chosen such that, it is optimal in one model, and efficient under rest of the models. Alternatively, a crossover design could be desirable which is highly efficient under all five models. The addition of placebo in comparing two active treatments reduces the variance of treatment contrast by 50%, under SBM. However, the gain is lesser under rest of the four models. Therefore, it is necessary to find crossover designs which are efficient under all five models. In class $COD(2+1, 3, 4)$, $cod(p)133$ is optimal under NCM, TSM and TBM, and, efficient under SSM and SBM with efficiencies 97% and 61% respectively. When 6 subjects are available, then $cod(p)140$\{AABB, APBP, BAPP, BBAA, PBPA, PPAB\} is useful because, this is the only design which has an efficiency of more than 65% in all five models. In class $COD(2+1, 9, 4)$, $cod(p)148$\{AABB, ABPP, APPB, 2BBAA, BPAP, PABP, PAPB, PPBA\} has an efficiency of more than 74% for each of five models. Crossover designs $cod(p)153$ and $cod(p)154$\{2AABB, 3ABBA, 3BAAB, 2BBAA\} in ten subjects are optimal under NCM, TSM, TBM and SSM but have very poor efficiency, only 42% under SBM. Since, $cod(p)149$\{AABB, ABBA, APBP, BAAB, BBAA,

BPAP, PAPB, PBPA, PPPP} and $cod(p)152${AABB, ABPP, APPB, 2BBAA, BPAP, PABP, PAPB, PPBA} in nine subjects have efficiencies more than 60%, they are efficient in all five models. Similarly, in the class $COD(2+1, 12, 4)$, $cod(p)157${3AABB, 3ABBA, 3BAAB, 3BBAA} is optimal under all models except SBM, because, it has very poor efficiency of 36% under SBM. Hence $cod(p)159${2ABPP, 2APBB, 2BAPP, 2BPAA, 2PABB, 2PBAA} and $cod(p)161${AABP, ABBP, 2APPB, BAAP, BBAP, 2BPPA, 2PABB, 2PBAA} having efficiencies more than 60% are a better choice in this case. Again as $cod(p)165$ in 14 subjects is optimal under all models except SBM, with only 42% efficiency under SBM, it is better to use an overall efficient design, $cod(p)164${AABP, ABBP, 2APPB, BAAP, BBAP, 2BPPA, 2PABB, 2PBAA} in 12 subjects, having an efficiency of more than 50% in all five models.