Supplementary Material of "Optimal allocation strategies in platform trials"

Design with concurrent and non-concurrent controls - Case 2

In this file, we provide the derivation of the optimal allocation for trials utilising concurrent and non-concurrent controls. Next, we focus on determining the optimal solutions for the Case 2 described in the paper.

For simplicity of calculation, in this file we start optimising using a different parametrization. We consider: r_{i,s} = n_{i,s} /N_s, where as before n_{i,s} is the sample size for arm i in the period s, and N_s is the total sample size in period s. At the end of the document we express the solutions in terms of p_{i,s} as in the paper.

Set conditions

```
In[1]:= subst = {r11 → r1 / 2 , r01 → r1 / 2 , r02 → (1 - r1) - r12 - r22 };

In[2]:= substp = {r12 → r2 p12, r22 → r2 p22, r02 → r2 p02, r3 → 1 - r1 - r2};
```

Define terms to optimise.

```
In[3]:= term1 = FullSimplify[(r11 * r01 / (r11 + r01)) + (r12 * r02 / (r12 + r02)) /. subst]
```

Out[3]= $$\frac{r1}{4} + r12 + \frac{r12^2}{-1 + r1 + r22}$$

```
In[4]:= term2 = FullSimplify[
  (1 / r22 + 1 / r02 - ((1 / r02) ^2 / (1 / r01 + 1 / r02 + 1 / r11 + 1 / r12))) ^ (-1) /. subst]
```

Out[4]= $$\frac{r22\,(r1^2 + 4\,r12\,(-1 + r12 + r22) + r1\,(-1 + 4\,r12 + r22))}{r1^2 + 4\,(-1 + r12)\,r12 + r1\,(-1 + 4\,r12)}$$

```
In[5]:= sol = Solve[term1 == term2, r12] [[3]]
```

Out[5]= $$\left\{r12 \to \frac{1}{2}\left(1 - r1 - \sqrt{1 - r1 - 4\,r22 + 4\,r1\,r22 + 4\,r22^2}\right)\right\}$$

```
In[6]:= term3 = Simplify[term1 /. sol]
```

Out[6]= $$\frac{r22\left(-2 + 3\,r1 + 4\,r22 - 2\sqrt{(1 - 2\,r22)^2 + r1\,(-1 + 4\,r22)}\right)}{4\,(-1 + r1 + r22)}$$

In[7]:= `derivative = FullSimplify[D[term3, r22]]`

Out[7]=
$$\frac{1}{4\,(-1+r1+r22)^2}\left(r22\,(-1+r1+r22)\left(4-\frac{4\,(-1+r1+2\,r22)}{\sqrt{(1-2\,r22)^2+r1\,(-1+4\,r22)}}\right)-r22\left(-2+3\,r1+4\,r22-2\,\sqrt{(1-2\,r22)^2+r1\,(-1+4\,r22)}\right)+(-1+r1+r22)\left(-2+3\,r1+4\,r22-2\,\sqrt{(1-2\,r22)^2+r1\,(-1+4\,r22)}\right)\right)$$

In[8]:= `sol2 = Solve[derivative == 0, r22];`

Solve: There may be values of the parameters for which some or all solutions are not valid.

In[9]:= `sol22 = Assuming[{r1 > 0, r1 < 1/2}, Simplify[sol2⟦3⟧]]`

Out[9]=
$$\Bigg\{r22\to 1-r1+\frac{1}{4\sqrt{3}}\left(\sqrt{\left(\left((-1+r1)\left(9\,r1^2+6\,r1\left(-4+\left(8+36\,r1-108\,r1^2+27\,r1^3+6\sqrt{3}\sqrt{r1\,(16-72\,r1+108\,r1^2-27\,r1^3)}\right)^{1/3}\right)+\left(-2+\left(8+36\,r1-108\,r1^2+27\,r1^3+6\sqrt{3}\sqrt{r1\,(16-72\,r1+108\,r1^2-27\,r1^3)}\right)^{1/3}\right)^2\right)\right)\Big/\left(8+36\,r1-108\,r1^2+27\,r1^3+6\sqrt{3}\sqrt{r1\,(16-72\,r1+108\,r1^2-27\,r1^3)}\right)^{1/3}\right)}-\frac{1}{2}\sqrt{\left(-\frac{22}{3}+8\,(-1+r1)^2+\frac{43\,r1}{3}-7\,r1^2-\frac{(-1+r1)\,(4-24\,r1+9\,r1^2)}{12\left(8+36\,r1-108\,r1^2+27\,r1^3+6\sqrt{3}\sqrt{r1\,(16-72\,r1+108\,r1^2-27\,r1^3)}\right)^{1/3}}-\frac{1}{12}(-1+r1)\left(8+36\,r1-108\,r1^2+27\,r1^3+6\sqrt{3}\sqrt{r1\,(16-72\,r1+108\,r1^2-27\,r1^3)}\right)^{1/3}+\left(\sqrt{3}\,(-1+r1)^2\,r1\left(8+36\,r1-108\,r1^2+27\,r1^3+6\sqrt{3}\sqrt{r1\,(16-72\,r1+108\,r1^2-27\,r1^3)}\right)^{1/6}\right)\Big/\left(\sqrt{\left((-1+r1)\left(9\,r1^2+6\,r1\left(-4+\left(8+36\,r1-108\,r1^2+27\,r1^3+6\sqrt{3}\sqrt{r1\,(16-72\,r1+108\,r1^2-27\,r1^3)}\right)^{1/3}\right)+\left(-2+\left(8+36\,r1-108\,r1^2+27\,r1^3+6\sqrt{3}\sqrt{r1\,(16-72\,r1+108\,r1^2-27\,r1^3)}\right)^{1/3}\right)^2\right)\right)}\right)\right)}\right)\Bigg\}$$

In[10]:=
```
CForm[sol22[[1]][[2]]]
```

Out[10]//CForm=
```
1 - r1 + Sqrt(((-1 + r1)*(9*Power(r1,2) + 6*r1*(-4 + Power(8 + 36*r1 - 108*Power(r1,2)
                0.3333333333333333)) + Power(-2 + Power(8 + 36*r1 - 108*Power(r1,2) + 27*
               0.3333333333333333),2)))/Power(8 + 36*r1 - 108*Power(r1,2) + 27*Power(r1,3
     (4.*Sqrt(3)) - Sqrt(-7.333333333333333 + 8*Power(-1 + r1,2) + (43*r1)/3. - 7*Power
       ((-1 + r1)*(4 - 24*r1 + 9*Power(r1,2)))/
        (12.*Power(8 + 36*r1 - 108*Power(r1,2) + 27*Power(r1,3) + 6*Sqrt(3)*Sqrt(r1*(16
       ((-1 + r1)*Power(8 + 36*r1 - 108*Power(r1,2) + 27*Power(r1,3) + 6*Sqrt(3)*Sqrt(r
       (Sqrt(3)*Power(-1 + r1,2)*r1*Power(8 + 36*r1 - 108*Power(r1,2) + 27*Power(r1,3)
        Sqrt((-1 + r1)*(9*Power(r1,2) + 6*r1*(-4 + Power(8 + 36*r1 - 108*Power(r1,2) +
                 0.3333333333333333)) + Power(-2 + Power(8 + 36*r1 - 108*Power(r1,2) + 27
                0.3333333333333333),2))))/2.
```

In[11]:=
```
sol22 /. {r1 → 0.3, r2 → 0.7}
```

Out[11]= {r22 → 0.302281}

Next, we simplify the solution by defining terms a and b.

In[12]:=
$$\text{sol22a} = \text{FullSimplify}\left[\text{sol22} \,/.\, \left\{\text{FullSimplify}\left[\left(8 + 36\,r1 - 108\,r1^2 + 27\,r1^3 + 6\sqrt{3}\sqrt{r1\left(16 - 72\,r1 + 108\,r1^2 - 27\,r1^3\right)}\right)^{1/3}\right] \to a\right\}\right]$$

Out[12]=
$$\left\{r22 \to 1 - r1 + \frac{1}{4\sqrt{3}}\left(\sqrt{\left(\left((-1+r1)\left(9\,r1^2 + 6\,r1\left(-4 + \left(8 + 9\,r1\,(4 + 3\,(-4+r1)\,r1) + 6\sqrt{3}\sqrt{r1\,(16 - 9\,r1\,(8 + 3\,(-4+r1)\,r1))}\right)^{1/3}\right) + \left(-2 + \left(8 + 9\,r1\,(4 + 3\,(-4+r1)\,r1) + 6\sqrt{3}\sqrt{r1\,(16 - 9\,r1\,(8 + 3\,(-4+r1)\,r1))}\right)^{1/3}\right)^2\right)\right) \Big/ \left(8 + 9\,r1\,(4 + 3\,(-4+r1)\,r1) + 6\sqrt{3}\sqrt{r1\,(16 - 9\,r1\,(8 + 3\,(-4+r1)\,r1))}\right)^{1/3}\right)}\right) - \frac{1}{2}\sqrt{\left(-\frac{22}{3} + 8\,(-1+r1)^2 + \frac{43\,r1}{3} - 7\,r1^2 - \frac{(-1+r1)\,(4 + 3\,r1\,(-8 + 3\,r1))}{12\left(8 + 9\,r1\,(4 + 3\,(-4+r1)\,r1) + 6\sqrt{3}\sqrt{r1\,(16 - 9\,r1\,(8 + 3\,(-4+r1)\,r1))}\right)^{1/3}} - \frac{1}{12}(-1+r1)\left(8 + 9\,r1\,(4 + 3\,(-4+r1)\,r1) + 6\sqrt{3}\sqrt{r1\,(16 - 9\,r1\,(8 + 3\,(-4+r1)\,r1))}\right)^{1/3} + \left(\sqrt{3}\,(-1+r1)^2\,r1\left(8 + 9\,r1\,(4 + 3\,(-4+r1)\,r1) + 6\sqrt{3}\sqrt{r1\,(16 - 9\,r1\,(8 + 3\,(-4+r1)\,r1))}\right)^{1/6}\right) \Big/ \left(\sqrt{\left((-1+r1)\left(9\,r1^2 + 6\,r1\left(-4 + \left(8 + 9\,r1\,(4 + 3\,(-4+r1)\,r1) + 6\sqrt{3}\sqrt{r1\,(16 - 9\,r1\,(8 + 3\,(-4+r1)\,r1))}\right)^{1/3}\right) + \left(-2 + \left(8 + 9\,r1\,(4 + 3\,(-4+r1)\,r1) + 6\sqrt{3}\sqrt{r1\,(16 - 9\,r1\,(8 + 3\,(-4+r1)\,r1))}\right)^{1/3}\right)^2\right)\right)}\right)\right)}\right\}$$

In[13]:=
$$\text{FullSimplify}\left[\left(8 + 9\,r1\,(4 + 3\,(-4+r1)\,r1) + 6\sqrt{3}\sqrt{r1\,(16 - 9\,r1\,(8 + 3\,(-4+r1)\,r1))}\right)^{1/3} \Big/ \left(8 + 36\,r1 - 108\,r1^2 + 27\,r1^3 + 6\sqrt{3}\sqrt{r1\left(16 - 72\,r1 + 108\,r1^2 - 27\,r1^3\right)}\right)^{1/3}\right]$$

Out[13]= 1

In[14]:= **sol22a /. $\left\{\left(8+9\,r1\,(4+3\,(-4+r1)\,r1)+6\sqrt{3}\sqrt{r1\,(16-9\,r1\,(8+3\,(-4+r1)\,r1))}\right)^{1/3}\to a\right\}$**

Out[14]=
$$\left\{r22\to 1-r1+\frac{\sqrt{\frac{(-1+r1)\left((-2+a)^2+6\,(-4+a)\,r1+9\,r1^2\right)}{\left(8+9\,r1\,(4+3\,(-4+r1)\,r1)+6\sqrt{3}\sqrt{r1\,(16-9\,r1\,(8+3\,(-4+r1)\,r1))}\right)^{1/3}}}}{4\sqrt{3}}-\frac{1}{2}\sqrt{\left(-\frac{22}{3}-\frac{1}{12}\,a\,(-1+r1)+8\,(-1+r1)^2+\frac{43\,r1}{3}-7\,r1^2-\frac{(-1+r1)\,(4+3\,r1\,(-8+3\,r1))}{12\left(8+9\,r1\,(4+3\,(-4+r1)\,r1)+6\sqrt{3}\sqrt{r1\,(16-9\,r1\,(8+3\,(-4+r1)\,r1))}\right)^{1/3}}+\left(\sqrt{3}\,(-1+r1)^2\,r1\left(8+9\,r1\,(4+3\,(-4+r1)\,r1)+6\sqrt{3}\sqrt{r1\,(16-9\,r1\,(8+3\,(-4+r1)\,r1))}\right)^{1/6}\right)\Big/\left(\sqrt{(-1+r1)\left((-2+a)^2+6\,(-4+a)\,r1+9\,r1^2\right)}\right)\right)}\right\}$$

In[15]:= **r22a = 1 - r1 + (√(((-1 + r1) ((-2 + a)^2 + 6 (-4 + a) r1 + 9 r1^2)) / a)) / (4 × √3) -
(1 / 2) √(- (22 / 3) - (1 / 12) a (-1 + r1) + 8 (-1 + r1)^2 +
(43 r1) / 3 - 7 r1^2 - ((-1 + r1) (4 + 3 r1 (-8 + 3 r1))) / (12 a) +
(√3 (-1 + r1)^2 r1 (a^3)^(1/6)) / (√((-1 + r1) ((-2 + a)^2 + 6 (-4 + a) r1 + 9 r1^2))))**

Out[15]=
$$1-r1+\frac{\sqrt{\frac{(-1+r1)\left((-2+a)^2+6\,(-4+a)\,r1+9\,r1^2\right)}{a}}}{4\sqrt{3}}-\frac{1}{2}\sqrt{\left(-\frac{22}{3}-\frac{1}{12}\,a\,(-1+r1)+8\,(-1+r1)^2+\frac{43\,r1}{3}-7\,r1^2+\frac{\sqrt{3}\,\left(a^3\right)^{1/6}\,(-1+r1)^2\,r1}{\sqrt{(-1+r1)\left((-2+a)^2+6\,(-4+a)\,r1+9\,r1^2\right)}}-\frac{(-1+r1)\,(4+3\,r1\,(-8+3\,r1))}{12\,a}\right)}$$

In[16]:= **CForm[r22a]**

Out[16]//CForm=

```
1 - r1 + Sqrt(((-1 + r1)*(Power(-2 + a,2) + 6*(-4 + a)*r1 + 9*Power(r1,2)))/a)/(4.*Sq
   Sqrt(-7.333333333333333 - (a*(-1 + r1))/12. + 8*Power(-1 + r1,2) + (43*r1)/3. - 7*P
      (Sqrt(3)*Power(Power(a,3),0.16666666666666666)*Power(-1 + r1,2)*r1)/Sqrt((-1 + r
    2.
```

In[17]:= **FullSimplify[r22a]**

Out[17]=
$$1-r1+\frac{\sqrt{\frac{(-1+r1)\left((-2+a)^2+6\,(-4+a)\,r1+9\,r1^2\right)}{a}}}{4\sqrt{3}}-\frac{1}{2}\sqrt{\left(-\frac{22}{3}-\frac{1}{12}\,a\,(-1+r1)+8\,(-1+r1)^2+\frac{43\,r1}{3}-7\,r1^2+\frac{\sqrt{3}\,\left(a^3\right)^{1/6}\,(-1+r1)^2\,r1}{\sqrt{(-1+r1)\left((-2+a)^2+6\,(-4+a)\,r1+9\,r1^2\right)}}-\frac{(-1+r1)\,(4+3\,r1\,(-8+3\,r1))}{12\,a}\right)}$$

In[18]:= **sol22ab = FullSimplify[r22a /. {(-2 + a)^2 + 6 (-4 + a) r1 + 9 r1^2 → b}]**

Out[18]=
$$\frac{1}{12}\left(12+\sqrt{3}\sqrt{\frac{b\,(-1+r1)}{a}}-12\,r1-\sqrt{3}\sqrt{-\frac{(-1+r1)\left(-12\sqrt{3}\,a\left(a^3\right)^{1/6}\sqrt{b\,(-1+r1)}\,r1+b\left(4+8\,a+a^2-12\,(2+a)\,r1+9\,r1^2\right)\right)}{a\,b}}\right)$$

In[19]:= **sol22abs = FullSimplify[PowerExpand[r22a /. {(-2 + a)^2 + 6 (-4 + a) r1 + 9 r1^2 → b}]]**

Out[19]=
$$\frac{1}{12}\left(12+\frac{\sqrt{3}\,\sqrt{b}\,\sqrt{-1+r1}}{\sqrt{a}}-12\,r1-\sqrt{3}\sqrt{-\frac{(-1+r1)\left(-12\sqrt{3}\,a^{3/2}\sqrt{-1+r1}\,r1+\sqrt{b}\left(4+8\,a+a^2-12\,(2+a)\,r1+9\,r1^2\right)\right)}{a\,\sqrt{b}}}\right)$$

In[20]:= **CForm[sol22ab]**

Out[20]//CForm=

```
(12 + Sqrt(3)*Sqrt((b*(-1 + r1))/a) - 12*r1 - Sqrt(3)*Sqrt(-(((-1 + r1)*(-12*Sqrt(3)*
        b*(4 + 8*a + Power(a,2) - 12*(2 + a)*r1 + 9*Power(r1,2))))/(a*b))))/12.
```

We compute the solution in terms of p22 by taking into account that p22=r22/(1-r1), as 1-r1=r2 in this case.

In[21]:= **solp22 = FullSimplify[sol22ab / (1 - r1)]**

Out[21]=
$$\frac{-12-\sqrt{3}\sqrt{\frac{b\,(-1+r1)}{a}}+12\,r1+\sqrt{3}\sqrt{-\frac{(-1+r1)\left(-12\sqrt{3}\,a\left(a^3\right)^{1/6}\sqrt{b\,(-1+r1)}\,r1+b\left(4+8\,a+a^2-12\,(2+a)\,r1+9\,r1^2\right)\right)}{a\,b}}}{12\,(-1+r1)}$$

In[22]:= **CForm[solp22]**

Out[22]//CForm=

```
(-12 - Sqrt(3)*Sqrt((b*(-1 + r1))/a) + 12*r1 + Sqrt(3)*Sqrt(-(((-1 + r1)*(-12*Sqrt(3)
        b*(4 + 8*a + Power(a,2) - 12*(2 + a)*r1 + 9*Power(r1,2))))/(a*b))))/(12
```

Simplifying solution p22

First note that a>0 and b<0

In[23]:= $\left(8+9\,r1\,(4+3\,(-4+r1)\,r1)+6\sqrt{3}\sqrt{r1\,(16-9\,r1\,(8+3\,(-4+r1)\,r1))}\right)^{1/3}$ /. {r1 → 0.3}

Out[23]= 2.72751

In[24]:= $(-2+a)^2+6\,(-4+a)\,r1+9\,r1^2$ /. {r1 → 0.3, a → 2.727510816380422}

Out[24]= −0.951209

In[25]:=
$$\text{FullSimplify}\left[\frac{-12+12\,r1}{12\,(-1+r1)}\right]+\text{FullSimplify}\left[\frac{-\sqrt{3}\sqrt{b\,(-1+r1)/a}+\sqrt{3}\sqrt{-\frac{(-1+r1)\left(-12\sqrt{3}\,a\,(a^3)^{1/6}\sqrt{b\,(-1+r1)}\,r1+b\left(4+8\,a+a^2-12\,(2+a)\,r1+9\,r1^2\right)\right)}{a\,b}}}{12\,(-1+r1)}\right]$$

Out[25]=
$$1+\frac{-\sqrt{\frac{b\,(-1+r1)}{a}}+\sqrt{-\frac{(-1+r1)\left(-12\sqrt{3}\,a\,(a^3)^{1/6}\sqrt{b\,(-1+r1)}\,r1+b\left(4+8\,a+a^2-12\,(2+a)\,r1+9\,r1^2\right)\right)}{a\,b}}}{4\sqrt{3}\,(-1+r1)}$$

In[26]:= solp22s = Assuming[{a > 0, b < 0, r1 < 1, r1 > 0},
$$\text{FullSimplify}\left[1+\frac{-\sqrt{\frac{b\,(-1+r1)}{a}}+\sqrt{-\frac{(-1+r1)\left(-12\sqrt{3}\,a\,(a^3)^{1/6}\sqrt{b\,(-1+r1)}\,r1+b\left(4+8\,a+a^2-12\,(2+a)\,r1+9\,r1^2\right)\right)}{a\,b}}}{4\sqrt{3}\,(-1+r1)}\right]\Big]$$

Out[26]=
$$1+\frac{-\sqrt{\frac{b\,(-1+r1)}{a}}+\sqrt{-\frac{(-1+r1)\left(-12\sqrt{3}\sqrt{a^3\,b\,(-1+r1)}\,r1+b\left(4+8\,a+a^2-12\,(2+a)\,r1+9\,r1^2\right)\right)}{a\,b}}}{4\sqrt{3}\,(-1+r1)}$$

In[27]:=
$$\text{solp22s2} = 1+\frac{\sqrt{-b}-\sqrt{12\sqrt{3}\sqrt{a^3\,b\verb|^|(-1)\,(-1+r1)}\,r1+\left(4+8\,a+a^2-12\,(2+a)\,r1+9\,r1^2\right)}}{4\sqrt{3\,a\,(1-r1)}}$$

Out[27]=
$$1+\frac{\sqrt{-b}-\sqrt{4+8\,a+a^2-12\,(2+a)\,r1+12\sqrt{3}\sqrt{\frac{a^3\,(-1+r1)}{b}}\,r1+9\,r1^2}}{4\sqrt{3}\sqrt{a\,(1-r1)}}$$

In[28]:= CForm[solp22s2]

Out[28]//CForm=
```
1 + (Sqrt(-b) - Sqrt(4 + 8*a + Power(a,2) - 12*(2 + a)*r1 + 12*Sqrt(3)*Sqrt((Power(a,3
```

In[29]:= solp22s /. {r1 → 0.3, a → 2.727510816380422`, b → -0.9512085425647322`}

Out[29]= 0.43183

In[30]:= solp22s2 /. {r1 → 0.3, a → 2.727510816380422`, b → -0.9512085425647322`}

Out[30]= 0.43183

In[31]:= Assuming[{a > 0, b < 0, r1 < 1, r1 > 0}, FullSimplify[solp22s / solp22]]

Out[31]= 1

Finally, to get the solution r12 (and hence p12), one needs to use the solution obtained for r22 and substitute it in the expression for r12 (***sol***).

In[32]:= **sol**

Out[32]= $$\left\{r12 \to \frac{1}{2}\left(1 - r1 - \sqrt{1 - r1 - 4\,r22 + 4\,r1\,r22 + 4\,r22^2}\right)\right\}$$

In[33]:= **solp22 = FullSimplify[sol[[1]][[2]] / (1 - r1) /. {r22 → p22 * (1 - r1)}]**

Out[33]= $$\frac{-1 + \sqrt{(-1 + 4\,(-1 + p22)\,p22\,(-1 + r1))\,(-1 + r1)} + r1}{2\,(-1 + r1)}$$

In[34]:= **solp22s = FullSimplify[solp22 /.**

$$\left\{p22 \to 1 + \frac{\sqrt{-b\,(1 - r1)} - \sqrt{\frac{(1-r1)\left(-12\,\sqrt{3}\,a\,(a^3)^{1/6}\,\sqrt{-b\,(1-r1)}\,r1 + b\,(4 + 8\,a + a^2 - 12\,(2 + a)\,r1 + 9\,r1^2)\right)}{b}}}{4\,\sqrt{3\,a}\,(1 - r1)}\right\}\Big]$$

Out[34]= $$\frac{1}{2} + \frac{1}{2\,(-1 + r1)}\left(\sqrt{\left((-1 + r1)\left(-1 + \frac{1}{12\,\sqrt{3}\,a\,(-1 + r1)}\left(\sqrt{b\,(-1 + r1)} - \sqrt{\left(-\frac{1}{b}(-1 + r1)\left(-12\,\sqrt{3}\,a\,(a^3)^{1/6}\,\sqrt{b\,(-1 + r1)}\,r1 + b\,(4 + 8\,a + a^2 - 12\,(2 + a)\,r1 + 9\,r1^2)\right)\right)}\right)\left(-12\,\sqrt{a}\,(-1 + r1) + \sqrt{3}\left(\sqrt{b\,(-1 + r1)} - \sqrt{\left(-\frac{1}{b}(-1 + r1)\left(-12\,\sqrt{3}\,a\,(a^3)^{1/6}\,\sqrt{b\,(-1 + r1)}\,r1 + b\,(4 + 8\,a + a^2 - 12\,(2 + a)\,r1 + 9\,r1^2)\right)\right)}\right)\right)\right)\right)}\right)$$