

S1 Appendix. Simulation Code

```
##Alecia Nickless
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#Code to simulate datasets for HoNOS outcome
#Following procedure outlined in Song et al (2013)

#NULL models
##Simulation D1
nSim <- 1000
file_loc <- "C:/Users/aleci_000/Documents/Oxford Documents/Stepped Wedge Paper/Sim_Datasets/"

Sim0 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = -0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 0 #Time
    Beta2 <- 0 #Intervention
    Beta3 <- 0 #Intervention specific Time

    Patient_ID = NULL
    Time = NULL
    TimeInt = NULL
    Intervention = NULL
    HONOS_scores = NULL
    Cluster_ID = NULL
    Random_Error = NULL
    Random_Effect = NULL
    for (i in 1:NumCentre) {
      random_effect_clust <- rnorm(1,0,sigmac)
```

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for (k in 1:AverageClusterSize) {
  random_effect = rnorm(1,0,sigmab)
  for (j in 1:NSteps) {
    randomstart = match(i, random_centres) + 1
    patientnumber = (i - 1)*20 + k
    Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
    Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
    time = j
    Time = c(Time, j)
    random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
    if (j==1) {
      random_error_corr = random_error
    }
    if (j > 1) {
      random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
    }
    Random_Error = c(Random_Error, random_error_corr)
    Random_Effect = c(Random_Effect, random_effect)
    if (j < randomstart) {
      timeint = 0
      intervention = 0
    }
    else {
      timeint = j - randomstart + 1
      intervention = 1}
    TimeInt = c(TimeInt, timeint)
    Intervention = c(Intervention, intervention)
    HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_effect_clust +
random_error_corr
    HONOS_scores <- c(HONOS_scores, HONOS)
  }
}
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim0_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim0(nSim)

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##Simulation D2
Sim0000 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = 0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 0 #Time
    Beta2 <- 0 #Intervention
    Beta3 <- 0 #Intervention specific Time

    Patient_ID = NULL
    Time = NULL
    TimeInt = NULL
    Intervention = NULL
    HONOS_scores = NULL
    Cluster_ID = NULL
    Random_Error = NULL
    Random_Effect = NULL
    for (i in 1:NumCentre) {
      random_effect_clust <- rnorm(1,0,sigmac)
      for (k in 1:AverageClusterSize) {
        random_effect = rnorm(1,0,sigmab)
        for (j in 1:NSteps) {
          randomstart = match(i, random_centres) + 1
          patientnumber = (i - 1)*20 + k
          Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
          Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
          time = j
          Time = c(Time, j)
          random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
          if (j==1) {

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        random_error_corr = random_error
    }
    if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
    }
    Random_Error = c(Random_Error, random_error_corr)
    Random_Effect = c(Random_Effect, random_effect)
    if (j < randomstart) {
        timeint = 0
        intervention = 0
    }
    else {
        timeint = j - randomstart + 1
        intervention = 1}
    TimeInt = c(TimeInt, timeint)
    Intervention = c(Intervention, intervention)
    HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_effect_clust +
random_error_corr
    HONOS_scores <- c(HONOS_scores, HONOS)
    }
}
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim0000_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim0000(nSim)

##Simulation D3
Sim00 <- function(nSim) {
  for (N in 1:nSim){

sigmab = 4.415
sigmae = 5.442
sigmac = 0.9570
rho = -0.5

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NumCentre = 12
NSteps = NumCentre + 1
AverageClusterSize = 20

centres = seq(1,NumCentre)
random_centres = sample(centres, NumCentre, replace = FALSE)

Beta0 <- 14.00 #Mean
Beta1 <- 0.25 #Time
Beta2 <- 0 #Intervention
Beta3 <- 0 #Intervention specific Time

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmas)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
      }
    }
  }
}

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        intervention = 0
    }
    else {
        timeint = j - randomstart + 1
        intervention = 1}
    TimeInt = c(TimeInt, timeint)
    Intervention = c(Intervention, intervention)
    HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_error_corr
    HONOS_scores <- c(HONOS_scores, HONOS)
}
}
}

```

```

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim00_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim00(nSim)

```

```

##Simulation D4
Sim00000 <- function(nSim) {
  for (N in 1:nSim){

    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = 0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 0.25 #Time

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Beta2 <- 0 #Intervention
Beta3 <- 0 #Intervention specific Time

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmac)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
        intervention = 0
      }
      else {
        timeint = j - randomstart + 1
        intervention = 1}
      TimeInt = c(TimeInt, timeint)
      Intervention = c(Intervention, intervention)
      HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_error_corr
      HONOS_scores <- c(HONOS_scores, HONOS)
    }
  }
}

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    }
  }

  dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
  dataset <- as.data.frame(dataset)
  write.csv(dataset, file = paste(file_loc,"Sim00000_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim00000(nSim)

##Simulation D5
Sim000 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = -0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 1 #Time
    Beta2 <- 0 #Intervention
    Beta3 <- 0 #Intervention specific Time

    x <- seq(0,12)
    y <- sin(x*180/12*pi/180)
    Beta1_time <- y*2*Beta1
    Beta3_time <- y*1*Beta3
    Time_factor <- seq(1,13)
    Time_factor <- factor(Time_factor)

    Patient_ID = NULL

```



```

Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmac)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
        intervention = 0
      }
      else {
        timeint = j - randomstart + 1
        intervention = 1}
      TimeInt = c(TimeInt, timeint)
      Intervention = c(Intervention, intervention)
      HONOS = Beta0 + Beta1_time[match(factor(time),Time_factor)] + Beta2*intervention +
Beta3_time[match(factor(time),Time_factor)] + random_effect + random_error_corr
      HONOS_scores <- c(HONOS_scores, HONOS)
    }
  }
}
}

```

```

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim000_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim000(nSim)

##Simulation D6
Sim000000 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = 0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 1 #Time
    Beta2 <- 0 #Intervention
    Beta3 <- 0 #Intervention specific Time

    x <- seq(0,12)
    y <- sin(x*180/12*pi/180)
    Beta1_time <- y*2*Beta1
    Beta3_time <- y*1*Beta3
    Time_factor <- seq(1,13)
    Time_factor <- factor(Time_factor)

    Patient_ID = NULL
    Time = NULL
    TimeInt = NULL
    Intervention = NULL

```

```

HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmab)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
        intervention = 0
      }
      else {
        timeint = j - randomstart + 1
        intervention = 1}
      TimeInt = c(TimeInt, timeint)
      Intervention = c(Intervention, intervention)
      HONOS = Beta0 + Beta1_time[match(factor(time),Time_factor)] + Beta2*intervention +
Beta3_time[match(factor(time),Time_factor)] + random_effect + random_error_corr
      HONOS_scores <- c(HONOS_scores, HONOS)
    }
  }
}
}

```

```
dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
```

```
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim000000_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim000000(nSim)
```

```
##Simulation D7
Sim0000000 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = -0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 1 #Time
    Beta2 <- 0 #Intervention
    Beta3 <- 0 #Intervention specific Time

    x <- seq(0,12)
    y <- sin(x*180/6*pi/180)
    Beta1_time <- y*2*Beta1
    Beta3_time <- y*1*Beta3
    Time_factor <- seq(1,13)
    Time_factor <- factor(Time_factor)

    Patient_ID = NULL
    Time = NULL
    TimeInt = NULL
    Intervention = NULL
    HONOS_scores = NULL
    Cluster_ID = NULL
```

```

Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmab)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
        intervention = 0
      }
      else {
        timeint = j - randomstart + 1
        intervention = 1}
      TimeInt = c(TimeInt, timeint)
      Intervention = c(Intervention, intervention)
      HONOS = Beta0 + Beta1_time[match(factor(time),Time_factor)] + Beta2*intervention +
Beta3_time[match(factor(time),Time_factor)] + random_effect + random_error_corr
      HONOS_scores <- c(HONOS_scores, HONOS)
    }
  }
}

```

```

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim0000000_",N,".csv", sep = ""))

```

```

}
}
set.seed(12345)
Sim0000000(nSim)

##Simulation D8
Sim000000000 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = 0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 1 #Time
    Beta2 <- 0 #Intervention
    Beta3 <- 0 #Intervention specific Time

    x <- seq(0,12)
    y <- sin(x*180/6*pi/180)
    Beta1_time <- y*2*Beta1
    Beta3_time <- y*1*Beta3
    Time_factor <- seq(1,13)
    Time_factor <- factor(Time_factor)

    Patient_ID = NULL
    Time = NULL
    TimeInt = NULL
    Intervention = NULL
    HONOS_scores = NULL
    Cluster_ID = NULL
    Random_Error = NULL
    Random_Effect = NULL
    for (i in 1:NumCentre) {

```

```

random_effect_clust <- rnorm(1,0,sigmac)
for (k in 1:AverageClusterSize) {
  random_effect = rnorm(1,0,sigmab)
  for (j in 1:NSteps) {
    randomstart = match(i, random_centres) + 1
    patientnumber = (i - 1)*20 + k
    Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
    Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
    time = j
    Time = c(Time, j)
    random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
    if (j==1) {
      random_error_corr = random_error
    }
    if (j > 1) {
      random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
    }
    Random_Error = c(Random_Error, random_error_corr)
    Random_Effect = c(Random_Effect, random_effect)
    if (j < randomstart) {
      timeint = 0
      intervention = 0
    }
    else {
      timeint = j - randomstart + 1
      intervention = 1}
    TimeInt = c(TimeInt, timeint)
    Intervention = c(Intervention, intervention)
    HONOS = Beta0 + Beta1_time[match(factor(time),Time_factor)] + Beta2*intervention +
Beta3_time[match(factor(time),Time_factor)] + random_effect + random_error_corr
    HONOS_scores <- c(HONOS_scores, HONOS)
  }
}
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim00000000_",N,".csv", sep = ""))
}
}
set.seed(12345)

```

```

Sim00000000(nSim)

#Intervention Models
##Simulation D9
Sim1 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = -0.5

NumCentre = 12
NSteps = NumCentre + 1
AverageClusterSize = 20

centres = seq(1,NumCentre)
random_centres = sample(centres, NumCentre, replace = FALSE)

Beta0 <- 14.00 #Mean
Beta1 <- 0 #Time
Beta2 <- 2 #Intervention
Beta3 <- 0 #Intervention specific Time

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmab)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j

```



```

Time = c(Time, j)
random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
if (j==1) {
  random_error_corr = random_error
}
if (j > 1) {
  random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
}
Random_Error = c(Random_Error, random_error_corr)
Random_Effect = c(Random_Effect, random_effect)
if (j < randomstart) {
  timeint = 0
  intervention = 0
}
else {
  timeint = j - randomstart + 1
  intervention = 1}
TimeInt = c(TimeInt, timeint)
Intervention = c(Intervention, intervention)
HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_error_corr
HONOS_scores <- c(HONOS_scores, HONOS)
}
}
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim1_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim1(nSim)

##Simulation D10
Sim5 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = 0.5

```

```

NumCentre = 12
NSteps = NumCentre + 1
AverageClusterSize = 20

centres = seq(1,NumCentre)
random_centres = sample(centres, NumCentre, replace = FALSE)

Beta0 <- 14.00 #Mean
Beta1 <- 0 #Time
Beta2 <- 2 #Intervention
Beta3 <- 0 #Intervention specific Time

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmac)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
      }
    }
  }
}

```

```

        intervention = 0
    }
    else {
        timeint = j - randomstart + 1
        intervention = 1}
    TimeInt = c(TimeInt, timeint)
    Intervention = c(Intervention, intervention)
    HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_error_corr
    HONOS_scores <- c(HONOS_scores, HONOS)
}
}
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim5_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim5(nSim)

##Simulation D11
Sim2 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = -0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 0.25 #Time
    Beta2 <- 2 #Intervention
    Beta3 <- 0 #Intervention specific Time

```

```

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmac)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
        intervention = 0
      }
      else {
        timeint = j - randomstart + 1
        intervention = 1}
      TimeInt = c(TimeInt, timeint)
      Intervention = c(Intervention, intervention)
      HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_error_corr
      HONOS_scores <- c(HONOS_scores, HONOS)
    }
  }
}

```

```

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim2_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim2(nSim)

##Simulation D12
Sim6 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = 0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 0.25 #Time
    Beta2 <- 2 #Intervention
    Beta3 <- 0 #Intervention specific Time

    Patient_ID = NULL
    Time = NULL
    TimeInt = NULL
    Intervention = NULL
    HONOS_scores = NULL
    Cluster_ID = NULL
    Random_Error = NULL
    Random_Effect = NULL
    for (i in 1:NumCentre) {
      random_effect_clust <- rnorm(1,0,sigmac)
      for (k in 1:AverageClusterSize) {
        random_effect = rnorm(1,0,sigmab)
        for (j in 1:NSteps) {

```

```

randomstart = match(i, random_centres) + 1
patientnumber = (i - 1)*20 + k
Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
time = j
Time = c(Time, j)
random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
if (j==1) {
  random_error_corr = random_error
}
if (j > 1) {
  random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
}
Random_Error = c(Random_Error, random_error_corr)
Random_Effect = c(Random_Effect, random_effect)
if (j < randomstart) {
  timeint = 0
  intervention = 0
}
else {
  timeint = j - randomstart + 1
  intervention = 1}
TimeInt = c(TimeInt, timeint)
Intervention = c(Intervention, intervention)
HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_error_corr
HONOS_scores <- c(HONOS_scores, HONOS)
}
}
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim6_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim6(nSim)

##Simulation D13
Sim3 <- function(nSim) {
  for (N in 1:nSim){

```

```

    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = -0.5

NumCentre = 12
NSteps = NumCentre + 1
AverageClusterSize = 20

centres = seq(1,NumCentre)
random_centres = sample(centres, NumCentre, replace = FALSE)

Beta0 <- 14.00 #Mean
Beta1 <- 0.25 #Time
Beta2 <- 2 #Intervention
Beta3 <- 0.15 #Intervention specific Time

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmab)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
    }
  }
}

```

```

Random_Error = c(Random_Error, random_error_corr)
Random_Effect = c(Random_Effect, random_effect)
if (j < randomstart) {
  timeint = 0
  intervention = 0
}
else {
  timeint = j - randomstart + 1
  intervention = 1}
TimeInt = c(TimeInt, timeint)
Intervention = c(Intervention, intervention)
HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_error_corr
HONOS_scores <- c(HONOS_scores, HONOS)
}
}
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim3_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim3(nSim)

##Simulation D14
Sim7 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = 0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 0.25 #Time

```



```

Beta2 <- 2 #Intervention
Beta3 <- 0.15 #Intervention specific Time

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmac)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
        intervention = 0
      }
      else {
        timeint = j - randomstart + 1
        intervention = 1}
      TimeInt = c(TimeInt, timeint)
      Intervention = c(Intervention, intervention)
      HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_error_corr
      HONOS_scores <- c(HONOS_scores, HONOS)
    }
  }
}

```

```

    }
  }

  dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
  dataset <- as.data.frame(dataset)
  write.csv(dataset, file = paste(file_loc,"Sim7_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim7(nSim)

##Simulation D15
Sim4 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = -0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 0.25 #Time
    Beta2 <- 0 #Intervention
    Beta3 <- 0.15 #Intervention specific Time

    Patient_ID = NULL
    Time = NULL
    TimeInt = NULL
    Intervention = NULL
    HONOS_scores = NULL
    Cluster_ID = NULL
    Random_Error = NULL
    Random_Effect = NULL
    for (i in 1:NumCentre) {
      random_effect_clust <- rnorm(1,0,sigmac)

```

```

for (k in 1:AverageClusterSize) {
  random_effect = rnorm(1,0,sigtab)
  for (j in 1:NSteps) {
    randomstart = match(i, random_centres) + 1
    patientnumber = (i - 1)*20 + k
    Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
    Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
    time = j
    Time = c(Time, j)
    random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
    if (j==1) {
      random_error_corr = random_error
    }
    if (j > 1) {
      random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
    }
    Random_Error = c(Random_Error, random_error_corr)
    Random_Effect = c(Random_Effect, random_effect)
    if (j < randomstart) {
      timeint = 0
      intervention = 0
    }
    else {
      timeint = j - randomstart + 1
      intervention = 1}
    TimeInt = c(TimeInt, timeint)
    Intervention = c(Intervention, intervention)
    HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_error_corr
    HONOS_scores <- c(HONOS_scores, HONOS)
  }
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim4_",N,".csv", sep =""))
}
}
set.seed(12345)
Sim4(nSim)

```

```

##Simulation D16
Sim8 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = 0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 0.25 #Time
    Beta2 <- 0 #Intervention
    Beta3 <- 0.15 #Intervention specific Time

    Patient_ID = NULL
    Time = NULL
    TimeInt = NULL
    Intervention = NULL
    HONOS_scores = NULL
    Cluster_ID = NULL
    Random_Error = NULL
    Random_Effect = NULL
    for (i in 1:NumCentre) {
      random_effect_clust <- rnorm(1,0,sigmac)
      for (k in 1:AverageClusterSize) {
        random_effect = rnorm(1,0,sigmab)
        for (j in 1:NSteps) {
          randomstart = match(i, random_centres) + 1
          patientnumber = (i - 1)*20 + k
          Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
          Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
          time = j
          Time = c(Time, j)
          random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
          if (j==1) {
            random_error_corr = random_error
          }
        }
      }
    }
  }
}

```

```

if (j > 1) {
  random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
}
Random_Error = c(Random_Error, random_error_corr)
Random_Effect = c(Random_Effect, random_effect)
if (j < randomstart) {
  timeint = 0
  intervention = 0
}
else {
  timeint = j - randomstart + 1
  intervention = 1}
TimeInt = c(TimeInt, timeint)
Intervention = c(Intervention, intervention)
HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_error_corr
HONOS_scores <- c(HONOS_scores, HONOS)
}
}
}

```

```

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim8_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim8(nSim)

```

```

##Simulation D17
Sim15 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = -0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)

```

```

random_centres = sample(centres, NumCentre, replace = FALSE)

Beta0 <- 14.00 #Mean
Beta1 <- 0.25 #Time
Beta2 <- 2 #Intervention
Beta3 <- 0.25 #Intervention specific Time

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmab)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
        intervention = 0
      }
      else {
        timeint = j - randomstart + 1
        intervention = 1}
      TimeInt = c(TimeInt, timeint)
    }
  }
}

```

```

        Intervention = c(Intervention, intervention)
        HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_error_corr
        HONOS_scores <- c(HONOS_scores, HONOS)
    }
}
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim15_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim15(nSim)

##Simulation D18
Sim16 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = 0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 0.25 #Time
    Beta2 <- 2 #Intervention
    Beta3 <- 0.25 #Intervention specific Time

    Patient_ID = NULL
    Time = NULL
    TimeInt = NULL
    Intervention = NULL
    HONOS_scores = NULL
    Cluster_ID = NULL
  }
}

```

```

Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigbab)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
        intervention = 0
      }
      else {
        timeint = j - randomstart + 1
        intervention = 1}
      TimeInt = c(TimeInt, timeint)
      Intervention = c(Intervention, intervention)
      HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_error_corr
      HONOS_scores <- c(HONOS_scores, HONOS)
    }
  }
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim16_",N,".csv", sep = ""))
}
}

```



```

set.seed(12345)
Sim16(nSim)

##Simulation D19
Sim17 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = -0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 0.25 #Time
    Beta2 <- 0 #Intervention
    Beta3 <- 0.25 #Intervention specific Time

    Patient_ID = NULL
    Time = NULL
    TimeInt = NULL
    Intervention = NULL
    HONOS_scores = NULL
    Cluster_ID = NULL
    Random_Error = NULL
    Random_Effect = NULL
    for (i in 1:NumCentre) {
      random_effect_clust <- rnorm(1,0,sigmac)
      for (k in 1:AverageClusterSize) {
        random_effect = rnorm(1,0,sigmab)
        for (j in 1:NSteps) {
          randomstart = match(i, random_centres) + 1
          patientnumber = (i - 1)*20 + k
          Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
          Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
          time = j
          Time = c(Time, j)
        }
      }
    }
  }
}

```

```

random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
if (j==1) {
  random_error_corr = random_error
}
if (j > 1) {
  random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
}
Random_Error = c(Random_Error, random_error_corr)
Random_Effect = c(Random_Effect, random_effect)
if (j < randomstart) {
  timeint = 0
  intervention = 0
}
else {
  timeint = j - randomstart + 1
  intervention = 1}
TimeInt = c(TimeInt, timeint)
Intervention = c(Intervention, intervention)
HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_error_corr
HONOS_scores <- c(HONOS_scores, HONOS)
}
}
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim17_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim17(nSim)

##Simulation D20
Sim18 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = 0.5

    NumCentre = 12

```

```

NSteps = NumCentre + 1
AverageClusterSize = 20

centres = seq(1,NumCentre)
random_centres = sample(centres, NumCentre, replace = FALSE)

Beta0 <- 14.00 #Mean
Beta1 <- 0.25 #Time
Beta2 <- 0 #Intervention
Beta3 <- 0.25 #Intervention specific Time

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmac)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
        intervention = 0
      }
    }
  }
}

```

```

    else {
      timeint = j - randomstart + 1
      intervention = 1}
    TimeInt = c(TimeInt, timeint)
    Intervention = c(Intervention, intervention)
    HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_error_corr
    HONOS_scores <- c(HONOS_scores, HONOS)
  }
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim18_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim18(nSim)

##Simulation D21
Sim19 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = -0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 0.25 #Time
    Beta2 <- -2 #Intervention
    Beta3 <- -0.5 #Intervention specific Time

    Patient_ID = NULL
    Time = NULL

```

```

TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmab)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
        intervention = 0
      }
      else {
        timeint = j - randomstart + 1
        intervention = 1}
      TimeInt = c(TimeInt, timeint)
      Intervention = c(Intervention, intervention)
      HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_error_corr
      HONOS_scores <- c(HONOS_scores, HONOS)
    }
  }
}

```

```

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)

```

```

    dataset <- as.data.frame(dataset)
    write.csv(dataset, file = paste(file_loc,"Sim19_",N,".csv", sep = ""))
  }
}
set.seed(12345)
Sim19(nSim)

##Simulation D22
Sim20 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = 0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 0.25 #Time
    Beta2 <- -2 #Intervention
    Beta3 <- -0.5 #Intervention specific Time

    Patient_ID = NULL
    Time = NULL
    TimeInt = NULL
    Intervention = NULL
    HONOS_scores = NULL
    Cluster_ID = NULL
    Random_Error = NULL
    Random_Effect = NULL
    for (i in 1:NumCentre) {
      random_effect_clust <- rnorm(1,0,sigmac)
      for (k in 1:AverageClusterSize) {
        random_effect = rnorm(1,0,sigmab)
        for (j in 1:NSteps) {
          randomstart = match(i, random_centres) + 1
          patientnumber = (i - 1)*20 + k

```

```

Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
time = j
Time = c(Time, j)
random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
if (j==1) {
  random_error_corr = random_error
}
if (j > 1) {
  random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
}
Random_Error = c(Random_Error, random_error_corr)
Random_Effect = c(Random_Effect, random_effect)
if (j < randomstart) {
  timeint = 0
  intervention = 0
}
else {
  timeint = j - randomstart + 1
  intervention = 1}
TimeInt = c(TimeInt, timeint)
Intervention = c(Intervention, intervention)
HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_error_corr
HONOS_scores <- c(HONOS_scores, HONOS)
}
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim20_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim20(nSim)

##Simulation D23
Sim21 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442

```

```

sigmac = 0.9570
rho = -0.5

NumCentre = 12
NSteps = NumCentre + 1
AverageClusterSize = 20

centres = seq(1,NumCentre)
random_centres = sample(centres, NumCentre, replace = FALSE)

Beta0 <- 14.00 #Mean
Beta1 <- 0.25 #Time
Beta2 <- 0 #Intervention
Beta3 <- -0.5 #Intervention specific Time

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmab)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
    }
  }
}

```



```

    if (j < randomstart) {
      timeint = 0
      intervention = 0
    }
    else {
      timeint = j - randomstart + 1
      intervention = 1}
    TimeInt = c(TimeInt, timeint)
    Intervention = c(Intervention, intervention)
    HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_error_corr
    HONOS_scores <- c(HONOS_scores, HONOS)
  }
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim21_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim21(nSim)

##Simulation D24
Sim22 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = 0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 0.25 #Time
    Beta2 <- 0 #Intervention

```

```

Beta3 <- -0.5 #Intervention specific Time

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmac)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
        intervention = 0
      }
      else {
        timeint = j - randomstart + 1
        intervention = 1}
      TimeInt = c(TimeInt, timeint)
      Intervention = c(Intervention, intervention)
      HONOS = Beta0 + Beta1*time + Beta2*intervention + Beta3*timeint + random_effect + random_error_corr
      HONOS_scores <- c(HONOS_scores, HONOS)
    }
  }
}

```

```

}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim22_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim22(nSim)

##Simulation D25
Sim9 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = -0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 1 #Time
    Beta2 <- 2 #Intervention
    Beta3 <- 0 #Intervention specific Time

    x <- seq(0,12)
    y <- sin(x*180/12*pi/180)
    Beta1_time <- y*2*Beta1
    Beta3_time <- y*1*Beta3
    Time_factor <- seq(1,13)
    Time_factor <- factor(Time_factor)

    Patient_ID = NULL
    Time = NULL
    TimeInt = NULL

```

```

Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmab)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
        intervention = 0
      }
      else {
        timeint = j - randomstart + 1
        intervention = 1}
      TimeInt = c(TimeInt, timeint)
      Intervention = c(Intervention, intervention)
      HONOS = Beta0 + Beta1_time[match(factor(time),Time_factor)] + Beta2*intervention +
Beta3_time[match(factor(time),Time_factor)] + random_effect + random_error_corr
      HONOS_scores <- c(HONOS_scores, HONOS)
    }
  }
}
}

```

```
dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
```

```

dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim9_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim9(nSim)

##Simulation D26
Sim12 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = 0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 1 #Time
    Beta2 <- 2 #Intervention
    Beta3 <- 0 #Intervention specific Time

    x <- seq(0,12)
    y <- sin(x*180/12*pi/180)
    Beta1_time <- y*2*Beta1
    Beta3_time <- y*1*Beta3
    Time_factor <- seq(1,13)
    Time_factor <- factor(Time_factor)

    Patient_ID = NULL
    Time = NULL
    TimeInt = NULL
    Intervention = NULL
    HONOS_scores = NULL
    Cluster_ID = NULL
    Random_Error = NULL

```

```

Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmac)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
        intervention = 0
      }
      else {
        timeint = j - randomstart + 1
        intervention = 1}
      TimeInt = c(TimeInt, timeint)
      Intervention = c(Intervention, intervention)
      HONOS = Beta0 + Beta1_time[match(factor(time),Time_factor)] + Beta2*intervention +
Beta3_time[match(factor(time),Time_factor)] + random_effect + random_error_corr
      HONOS_scores <- c(HONOS_scores, HONOS)
    }
  }
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim12_",N,".csv", sep = ""))
}
}

```

```

set.seed(12345)
Sim12(nSim)

##Simulation D27
Sim10 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = -0.5

NumCentre = 12
NSteps = NumCentre + 1
AverageClusterSize = 20

centres = seq(1,NumCentre)
random_centres = sample(centres, NumCentre, replace = FALSE)

Beta0 <- 14.00 #Mean
Beta1 <- 1 #Time
Beta2 <- 2 #Intervention
Beta3 <- 1 #Intervention specific Time

x <- seq(0,12)
y <- sin(x*180/12*pi/180)
Beta1_time <- y*2*Beta1
Beta3_time <- y*1*Beta3
Time_factor <- seq(1,13)
Time_factor <- factor(Time_factor)

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)

```

```

for (k in 1:AverageClusterSize) {
  random_effect = rnorm(1,0,sigmas)
  for (j in 1:NSteps) {
    randomstart = match(i, random_centres) + 1
    patientnumber = (i - 1)*20 + k
    Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
    Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
    time = j
    Time = c(Time, j)
    random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
    if (j==1) {
      random_error_corr = random_error
    }
    if (j > 1) {
      random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
    }
    Random_Error = c(Random_Error, random_error_corr)
    Random_Effect = c(Random_Effect, random_effect)
    if (j < randomstart) {
      timeint = 0
      intervention = 0
    }
    else {
      timeint = j - randomstart + 1
      intervention = 1}
    TimeInt = c(TimeInt, timeint)
    Intervention = c(Intervention, intervention)
    HONOS = Beta0 + Beta1_time[match(factor(time),Time_factor)] + Beta2*intervention +
Beta3_time[match(factor(timeint),Time_factor)] + random_effect + random_error_corr
    HONOS_scores <- c(HONOS_scores, HONOS)
  }
}
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim10_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim10(nSim)

```



```

##Simulation D28
Siml3 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = 0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 1 #Time
    Beta2 <- 2 #Intervention
    Beta3 <- 1 #Intervention specific Time

    x <- seq(0,12)
    y <- sin(x*180/12*pi/180)
    Beta1_time <- y*2*Beta1
    Beta3_time <- y*1*Beta3
    Time_factor <- seq(1,13)
    Time_factor <- factor(Time_factor)

    Patient_ID = NULL
    Time = NULL
    TimeInt = NULL
    Intervention = NULL
    HONOS_scores = NULL
    Cluster_ID = NULL
    Random_Error = NULL
    Random_Effect = NULL
    for (i in 1:NumCentre) {
      random_effect_clust <- rnorm(1,0,sigmac)
      for (k in 1:AverageClusterSize) {
        random_effect = rnorm(1,0,sigmab)
        for (j in 1:NSteps) {
          randomstart = match(i, random_centres) + 1

```

```

patientnumber = (i - 1)*20 + k
Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
time = j
Time = c(Time, j)
random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
if (j==1) {
  random_error_corr = random_error
}
if (j > 1) {
  random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
}
Random_Error = c(Random_Error, random_error_corr)
Random_Effect = c(Random_Effect, random_effect)
if (j < randomstart) {
  timeint = 0
  intervention = 0
}
else {
  timeint = j - randomstart + 1
  intervention = 1}
TimeInt = c(TimeInt, timeint)
Intervention = c(Intervention, intervention)
HONOS = Beta0 + Beta1_time[match(factor(time),Time_factor)] + Beta2*intervention +
Beta3_time[match(factor(timeint),Time_factor)] + random_effect + random_error_corr
HONOS_scores <- c(HONOS_scores, HONOS)
}
}
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim13_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim13(nSim)

##Simulation D29
Sim11 <- function(nSim) {
  for (N in 1:nSim){

```

```

    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = -0.5

NumCentre = 12
NSteps = NumCentre + 1
AverageClusterSize = 20

centres = seq(1,NumCentre)
random_centres = sample(centres, NumCentre, replace = FALSE)

Beta0 <- 14.00 #Mean
Beta1 <- 1 #Time
Beta2 <- 0 #Intervention
Beta3 <- 1 #Intervention specific Time

x <- seq(0,12)
y <- sin(x*180/12*pi/180)
Beta1_time <- y*2*Beta1
Beta3_time <- y*1*Beta3
Time_factor <- seq(1,13)
Time_factor <- factor(Time_factor)

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmab)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
    }
  }
}

```

```

Time = c(Time, j)
random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
if (j==1) {
  random_error_corr = random_error
}
if (j > 1) {
  random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
}
Random_Error = c(Random_Error, random_error_corr)
Random_Effect = c(Random_Effect, random_effect)
if (j < randomstart) {
  timeint = 0
  intervention = 0
}
else {
  timeint = j - randomstart + 1
  intervention = 1}
TimeInt = c(TimeInt, timeint)
Intervention = c(Intervention, intervention)
HONOS = Beta0 + Beta1_time[match(factor(time),Time_factor)] + Beta2*intervention +
Beta3_time[match(factor(timeint),Time_factor)] + random_effect + random_error_corr
HONOS_scores <- c(HONOS_scores, HONOS)
}
}
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim11_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim11(nSim)

##Simulation D30
Sim14 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = 0.5

```

```

NumCentre = 12
NSteps = NumCentre + 1
AverageClusterSize = 20

centres = seq(1,NumCentre)
random_centres = sample(centres, NumCentre, replace = FALSE)

Beta0 <- 14.00 #Mean
Beta1 <- 1 #Time
Beta2 <- 0 #Intervention
Beta3 <- 1 #Intervention specific Time

x <- seq(0,12)
y <- sin(x*180/12*pi/180)
Beta1_time <- y*2*Beta1
Beta3_time <- y*1*Beta3
Time_factor <- seq(1,13)
Time_factor <- factor(Time_factor)

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmac)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
    }
  }
}

```

```

}
if (j > 1) {
  random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
}
Random_Error = c(Random_Error, random_error_corr)
Random_Effect = c(Random_Effect, random_effect)
if (j < randomstart) {
  timeint = 0
  intervention = 0
}
else {
  timeint = j - randomstart + 1
  intervention = 1}
TimeInt = c(TimeInt, timeint)
Intervention = c(Intervention, intervention)
HONOS = Beta0 + Beta1_time[match(factor(time),Time_factor)] + Beta2*intervention +
Beta3_time[match(factor(timeint),Time_factor)] + random_effect + random_error_corr
HONOS_scores <- c(HONOS_scores, HONOS)
}
}
}

```

```

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim14_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim14(nSim)

```

```

##Simulation D31
Sim23 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = -0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

```

```

centres = seq(1,NumCentre)
random_centres = sample(centres, NumCentre, replace = FALSE)

Beta0 <- 14.00 #Mean
Beta1 <- 1 #Time
Beta2 <- 2 #Intervention
Beta3 <- 0 #Intervention specific Time

x <- seq(0,12)
y <- sin(x*180/6*pi/180)
Beta1_time <- y*2*Beta1
Beta3_time <- y*1*Beta3
Time_factor <- seq(1,13)
Time_factor <- factor(Time_factor)

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmab)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
    }
  }
}

```

```

    Random_Error = c(Random_Error, random_error_corr)
    Random_Effect = c(Random_Effect, random_effect)
    if (j < randomstart) {
      timeint = 0
      intervention = 0
    }
    else {
      timeint = j - randomstart + 1
      intervention = 1}
    TimeInt = c(TimeInt, timeint)
    Intervention = c(Intervention, intervention)
    HONOS = Beta0 + Beta1_time[match(factor(time),Time_factor)] + Beta2*intervention +
Beta3_time[match(factor(time),Time_factor)] + random_effect + random_error_corr
    HONOS_scores <- c(HONOS_scores, HONOS)
  }
}
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim23_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim23(nSim)

##Simulation D32
Sim26 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = 0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

```



```

Beta0 <- 14.00 #Mean
Beta1 <- 1 #Time
Beta2 <- 2 #Intervention
Beta3 <- 0 #Intervention specific Time

x <- seq(0,12)
y <- sin(x*180/6*pi/180)
Beta1_time <- y*2*Beta1
Beta3_time <- y*1*Beta3
Time_factor <- seq(1,13)
Time_factor <- factor(Time_factor)

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmac)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
      }
    }
  }
}

```

```

        intervention = 0
    }
    else {
        timeint = j - randomstart + 1
        intervention = 1}
    TimeInt = c(TimeInt, timeint)
    Intervention = c(Intervention, intervention)
    HONOS = Beta0 + Beta1_time[match(factor(time),Time_factor)] + Beta2*intervention +
Beta3_time[match(factor(time),Time_factor)] + random_effect + random_error_corr
    HONOS_scores <- c(HONOS_scores, HONOS)
    }
}
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim26_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim26(nSim)

##Simulation D33
Sim24 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = -0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 1 #Time
    Beta2 <- 2 #Intervention

```

```

Beta3 <- 1 #Intervention specific Time

x <- seq(0,12)
y <- sin(x*180/6*pi/180)
Beta1_time <- y*2*Beta1
Beta3_time <- y*1*Beta3
Time_factor <- seq(1,13)
Time_factor <- factor(Time_factor)

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmac)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
        intervention = 0
      }
      else {
        timeint = j - randomstart + 1
      }
    }
  }
}

```

```

        intervention = 1}
        TimeInt = c(TimeInt, timeint)
        Intervention = c(Intervention, intervention)
        HONOS = Beta0 + Beta1_time[match(factor(time),Time_factor)] + Beta2*intervention +
Beta3_time[match(factor(timeint),Time_factor)] + random_effect + random_error_corr
        HONOS_scores <- c(HONOS_scores, HONOS)
    }
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim24_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim24(nSim)

##Simulation D34
Sim27 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = 0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 1 #Time
    Beta2 <- 2 #Intervention
    Beta3 <- 1 #Intervention specific Time

    x <- seq(0,12)
    y <- sin(x*180/6*pi/180)

```

```

Beta1_time <- y*2*Beta1
Beta3_time <- y*1*Beta3
Time_factor <- seq(1,13)
Time_factor <- factor(Time_factor)

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmac)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
        intervention = 0
      }
      else {
        timeint = j - randomstart + 1
        intervention = 1}
      TimeInt = c(TimeInt, timeint)
      Intervention = c(Intervention, intervention)
    }
  }
}

```

```

        HONOS = Beta0 + Beta1_time[match(factor(time),Time_factor)] + Beta2*intervention +
Beta3_time[match(factor(timeint),Time_factor)] + random_effect + random_error_corr
        HONOS_scores <- c(HONOS_scores, HONOS)
    }
}
}

dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim27_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim27(nSim)

##Simulation D35
Sim25 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = -0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 1 #Time
    Beta2 <- 0 #Intervention
    Beta3 <- 1 #Intervention specific Time

    x <- seq(0,12)
    y <- sin(x*180/6*pi/180)
    Beta1_time <- y*2*Beta1
    Beta3_time <- y*1*Beta3
    Time_factor <- seq(1,13)

```

```

Time_factor <- factor(Time_factor)

Patient_ID = NULL
Time = NULL
TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmac)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
        intervention = 0
      }
      else {
        timeint = j - randomstart + 1
        intervention = 1}
      TimeInt = c(TimeInt, timeint)
      Intervention = c(Intervention, intervention)
      HONOS = Beta0 + Beta1_time[match(factor(time),Time_factor)] + Beta2*intervention +
Beta3_time[match(factor(timeint),Time_factor)] + random_effect + random_error_corr
      HONOS_scores <- c(HONOS_scores, HONOS)
    }
  }
}

```

```

    }
  }

  dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
  dataset <- as.data.frame(dataset)
  write.csv(dataset, file = paste(file_loc,"Sim25_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim25(nSim)

##Simulation D36
Sim28 <- function(nSim) {
  for (N in 1:nSim){
    sigmab = 4.415
    sigmae = 5.442
    sigmac = 0.9570
    rho = 0.5

    NumCentre = 12
    NSteps = NumCentre + 1
    AverageClusterSize = 20

    centres = seq(1,NumCentre)
    random_centres = sample(centres, NumCentre, replace = FALSE)

    Beta0 <- 14.00 #Mean
    Beta1 <- 1 #Time
    Beta2 <- 0 #Intervention
    Beta3 <- 1 #Intervention specific Time

    x <- seq(0,12)
    y <- sin(x*180/6*pi/180)
    Beta1_time <- y*2*Beta1
    Beta3_time <- y*1*Beta3
    Time_factor <- seq(1,13)
    Time_factor <- factor(Time_factor)

    Patient_ID = NULL
    Time = NULL
  }
}

```



```

TimeInt = NULL
Intervention = NULL
HONOS_scores = NULL
Cluster_ID = NULL
Random_Error = NULL
Random_Effect = NULL
for (i in 1:NumCentre) {
  random_effect_clust <- rnorm(1,0,sigmac)
  for (k in 1:AverageClusterSize) {
    random_effect = rnorm(1,0,sigmab)
    for (j in 1:NSteps) {
      randomstart = match(i, random_centres) + 1
      patientnumber = (i - 1)*20 + k
      Patient_ID = c(Patient_ID, paste("Patient_",patientnumber, sep=""))
      Cluster_ID = c(Cluster_ID, paste("Cluster_",i, sep=""))
      time = j
      Time = c(Time, j)
      random_error = rnorm(1,0,sqrt((1-rho^2)*sigmae^2))
      if (j==1) {
        random_error_corr = random_error
      }
      if (j > 1) {
        random_error_corr = rho*Random_Error[(patientnumber-1)*NSteps + 1] + random_error
      }
      Random_Error = c(Random_Error, random_error_corr)
      Random_Effect = c(Random_Effect, random_effect)
      if (j < randomstart) {
        timeint = 0
        intervention = 0
      }
      else {
        timeint = j - randomstart + 1
        intervention = 1}
      TimeInt = c(TimeInt, timeint)
      Intervention = c(Intervention, intervention)
      HONOS = Beta0 + Beta1_time[match(factor(time),Time_factor)] + Beta2*intervention +
Beta3_time[match(factor(timeint),Time_factor)] + random_effect + random_error_corr
      HONOS_scores <- c(HONOS_scores, HONOS)
    }
  }
}

```

```
dataset <- cbind(Patient_ID, Cluster_ID, Intervention, Time, TimeInt, HONOS_scores, Random_Effect, Random_Error)
dataset <- as.data.frame(dataset)
write.csv(dataset, file = paste(file_loc,"Sim28_",N,".csv", sep = ""))
}
}
set.seed(12345)
Sim28(nSim)
```