This is the example R-code for creating a dataset of 200 subjects with their unique adherence pattern and adherence rate of 50%.

```
#*Statements given after # symbol are the comments about the code
setwd("C:\\adh_50")
library (markovchain)
# Following code creates a list file which has 200 individual data file as a list, which will be merged to
#create a single file with 200 subjects
ndata<-200
sim_data<-list()
for(i in 1:ndata){
  DAY<-c(1:180) # Dosing block
  TIME<-DAY*24
  INPUT<-rep(150,180)
  statesNames<-c(1,0)

# Following section generates adherence pattern as zeros and ones based on the values of transition
#matrix. Markov chain package is used to generate these patterns. Values in transition matrix can be
#altered to generate various rates of adherence

  mcA<-new("markovchain", transitionMatrix=matrix(c(0.5,0.5,0.5,0.5),byrow=TRUE,
                                    nrow=2, dimnames=list(statesNames,statesNames)))
  adherence_50<-data.frame(rmarkovchain(n=180,object=mcA,t0=0))
  colnames (adherence_50)[colnames(adherence_50)=="rmarkovchain.n...180..object...mcA..t0...0."] <-
"adherence_50"
  adh_vector<-as.vector(adherence_50[,1])# converting adherence pattern as vector and numeric
  adh_numeric<-as.numeric(adh_vector)

  # Following section creates the needed variables for the dataset
  AMT<-INPUT*adh_numeric
  DV<-rep(0,180)
  MDV<-rep(1,180)
  CMT<-rep(1,180)
  CID<-rep(1,180)
  zerotime<-data.frame(CID=1,DAY=0,TIME=0,AMT=150,DV=0,MDV=1,CMT=1)
  dosing<-data.frame(CID,DAY,TIME,AMT,DV,MDV,CMT)
  dosing_complete<-rbind(zerotime,dosing)
  NWEEK<-c(0:28)#PD_sampling block
  WEEK<-rep(NWEEK,each=7)
  # PD sampling related information
  PDS_DAY<-(NWEEK*7)
  PDS_TIME<-(PDS_DAY*24)
  PDS_AMT<-rep (0,29)
  PDS_DV<-rep (0,29)
  PDS_MDV<-rep (0,29)
  PDS_CMT<-rep (4,29)
  PDS_ID<-rep (1,29)
  PD_SAMPLING<-
data.frame(PDS_ID,PDS_DAY,PDS_TIME,PDS_AMT,PDS_DV,PDS_MDV,PDS_CMT)
  colnames(PD_SAMPLING)<-c("CID","DAY","TIME","AMT","DV","MDV","CMT")
  # PK sampling related information
```

```
  PKS_ID<-rep(1,8)
  PKS_DAY<-rep(10,8)
  PKSS_TIME<-(PKS_DAY*24)
  NTIME<-c(0,2,4,6,8,10,12,24)
  PKS_TIME<-(PKSS_TIME+NTIME)
  PKS_INPUT<-rep(0,8)
  PKS_AMT<-rep(0,8)
  PKS_DV<-rep(0,8)
  PKS_MDV<-rep(0,8)
  PKS_CMT<-rep(2,8)
  PK_SAMPLING<-data.frame
(PKS_ID,PKS_DAY,PKS_TIME,PKS_AMT,PKS_DV,PKS_MDV,PKS_CMT)
  colnames(PK_SAMPLING)<-c("CID","DAY","TIME","AMT","DV","MDV","CMT")
  DATA_SET<-rbind(dosing_complete,PD_SAMPLING,PK_SAMPLING)#Merging all blocks for
complete data set
  DATA_SET_FINAL<-DATA_SET [order(DATA_SET$CID, DATA_SET$DAY),]
  sim_data[[i]]<-DATA_SET_FINAL
  write.csv(sim_data[[i]],paste("C:\\adh_50\\sim_data",i,".csv",sep=""), row.names=F,quote=F)
}
#merging all data files with various adherence pattern to single data file
setwd("C:\\adh_50")
data <- lapply(dir(),read.csv)
data_new<-do.call("rbind",data)
id<-c(1:200)
id1<-rep(id, each=218)
id1<-as.data.frame(id1)
data_Modif<-cbind(id1,data_new)
sim_data <- data_Modif[ c(1,3:8) ]
colnames(sim_data)<-c("CID","DAY","TIME","AMT","DV","MDV","CMT")
write.csv (sim_data,"sim_data_50.csv",row.names=FALSE)
```

Model file: This is the example model file used to simulate PK-PD characteristic of long half-life and rapid onset PD onset (AC) group. Values for the parameters were used as per Table.1 to create other PK-PD characteristics of AD, BC & BD

```
; SIMULATION OF CLINICAL TRIAL WITH DIFFERENT PK-PD CHARACTERISTICS
$PROBLEM ADHERENCE MODEL TRIAL
$INPUT ID DAY TIME AMT DV MDV CMT
$DATA sim_data_50.csv IGNORE=@
$SUBROUTINE ADVAN6 TOL=3
$MODEL NCOMP=4 COMP=(GUT)COMP=(CENTRAL) COMP=(PERIPH) COMP=(EFFECT)
$PK
; PK MODEL
V2 = THETA (1)*EXP (ETA (1))
CL = THETA (2)*EXP (ETA (2))
KA = THETA (3)
Q= THETA (4)
V3= THETA (5)
```

```
K20 = CL/V2
K23 = Q/V2
K32 = Q/V3
S2 = V2/1000
; PD MODEL
TVKIN = THETA (6)
TVKOUT = THETA (7)
TVIC50 = THETA (8)
KIN = TVKIN * EXP (ETA (3))
KOUT = TVKOUT * EXP (ETA (4))
IC50 = TVIC50 * EXP (ETA (5))
A_0 (4) = KIN/KOUT
$DES
DADT (1) = -KA * A(1)
DADT (2) = (KA * A (1)) - ((K20 + K23) * A (2)) + (K32 * A(3))
DADT (3) = K23 * A (2) - K32 * A (3)
CP = A (2)/S2
INH = 1- (CP / (IC50 + CP)); Inhibitory function
DADT (4) = (KIN * INH) - KOUT * A (4)
$THETA
 534 FIX; central volume
 50 FIX; Clearance
 1 FIX; KA
 144 FIX; Q
 1530 FIX; Peripheral volume
 1 FIX; KIN (viral cells produced per hour)
 0.0165 FIX; KOUT (viral cells eliminated per hour)
 1 FIX
$OMEGA 0.1 FIX; V2
 0.1 FIX; CL
 0.16 FIX; KIN
 0.16 FIX; KOUT
 0.16 FIX; IC50
$ERROR
IPRED=F
REPI = IREP; simulation replication index
IF (A (4).LT.0) IPRED =0.01
Y=F*EXP (EPS (1))
$SIGMA
0.1 FIX
$SIMULATION (23457) ONLYSIMULATION NSUBPROBLEMS=1
$TABLE ID TIME DAY DV REPI PRED CMT NOPRINT NOHEADER FILE=test.txt
```