MODEL RUNS FOR FDA APPROVAL TIME REGRESSIONS, ADDING SHARED FRAILTIES FOR PRIMARY INDICATION OF THE DRUG, AND FIXED (COEFFICIENT VECTOR) EFFECTS FOR SPONSORING FIRMS.

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These models were estimated in STATA 8.0.

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. streg fsubmits orderent stafcder prevgenx lethal deathrt1 hosp01 hospdisc hho
> sleng acutediz orphdum natreg natregsq wpnoavg3 maxbudg1 mbudord1,  dist(logn
> ormal) frailty(invgaussian) shared(discode)

         failure _d:  aprovdum
   analysis time _t:  acttime

Fitting comparison lnormal model:

Fitting constant-only model:

Iteration 0:   log likelihood = -432.70794  (not concave)
Iteration 1:   log likelihood = -382.53802
Iteration 2:   log likelihood = -380.90867
Iteration 3:   log likelihood = -380.79745
Iteration 4:   log likelihood = -380.79726
Iteration 5:   log likelihood = -380.79726

Fitting full model:

Iteration 0:   log likelihood = -341.57081
Iteration 1:   log likelihood = -337.01341
Iteration 2:   log likelihood = -328.88885
Iteration 3:   log likelihood = -328.45001
Iteration 4:   log likelihood = -328.44309
Iteration 5:   log likelihood = -328.44309

Log-normal regression --
         accelerated failure-time form         Number of obs      =       300
         Inverse-Gaussian shared frailty       Number of groups   =        78
Group variable: discode

No. of subjects =          300                 Obs per group: min =         1
No. of failures =          249                                avg =  3.846154
Time at risk    =  8723.901362                                max =        47

                                               LR chi2(15)        =    104.71
Log likelihood  =   -328.44309                 Prob > chi2        =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    fsubmits |  -.0238646   .0077526    -3.08   0.002    -.0390593   -.0086698
    orderent |    .080062   .0267695     2.99   0.003     .0275947    .1325293
    stafcder |  -.0016454    .000228    -7.22   0.000    -.0020922   -.0011986
    prevgenx |   .0024467   .0008123     3.01   0.003     .0008546    .0040388
      lethal |  -.1186284   .1775378    -0.67   0.504    -.4665961    .2293393
    deathrt1 |  -.2134493   .1702151    -1.25   0.210    -.5470647    .1201662
      hosp01 |   .2594689   .2013185     1.29   0.197    -.1351081    .6540458
    hospdisc |   2.95e-07   5.57e-07     0.53   0.597    -7.96e-07    1.39e-06
    hhosleng |  -.0198767   .0154939    -1.28   0.200    -.0502442    .0104908
    acutediz |  -.0829098   .1623145    -0.51   0.609    -.4010404    .2352208
     orphdum |   .0581886   .1364711     0.43   0.670    -.2092898     .325667
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      natreg |   .0136462   .0072501     1.88   0.060    -.0005638    .0278562
    natregsq |  -.0000504   .0000397    -1.27   0.204    -.0001282    .0000273
    wpnoavg3 |  -.0020875   .0007191    -2.90   0.004    -.0034969   -.0006782
    maxbudg1 |   8.78e-10   1.19e-09     0.74   0.461    -1.46e-09    3.21e-09
    mbudord1 |  -2.69e-10   1.04e-10    -2.58   0.010    -4.74e-10   -6.47e-11
       _cons |   4.872893   .3135687    15.54   0.000      4.25831    5.487476
-------------+----------------------------------------------------------------
     /ln_sig |  -.3140049   .0572799    -5.48   0.000    -.4262714   -.2017384
     /ln_the |  -1.351387   .6108218    -2.21   0.027    -2.548576   -.1541982
-------------+----------------------------------------------------------------
       sigma |   .7305154   .0418438                      .6529391    .8173087
       theta |   .2588809   .1581301                      .0781929    .8571021
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =     6.84 Prob>=chibar2 = 0.004

. mfx compute, dydx

Marginal effects after lnormalhet
      y  = predicted median _t (predict)
         =  21.025602
------------------------------------------------------------------------------
variable |      dy/dx    Std. Err.     z    P>|z|  [    95% C.I.   ]      X
---------+--------------------------------------------------------------------
fsubmits |  -.5017672      .16855   -2.98   0.003  -.832111 -.171423   6.31333
orderent |   1.683351      .57515    2.93   0.003   .556071  2.81063   9.46333
stafcder |   -.034595      .00541   -6.40   0.000  -.045193 -.023997   1365.73
prevgenx |   .0514435      .01739    2.96   0.003   .017362  .085525   57.8241
  lethal*|  -2.557639      3.9328   -0.65   0.515  -10.2658  5.15051   .706667
deathrt1 |    -4.4879      3.6313   -1.24   0.216  -11.6051  2.62932   .120042
  hosp01*|   5.122762     3.79547    1.35   0.177  -2.31622  12.5617   .753333
hospdisc |   6.19e-06      .00001    0.53   0.596  -.000017  .000029    117530
hhosleng |  -.4179191      .32928   -1.27   0.204   -1.0633  .227466   4.07593
acutediz*|  -1.715526     3.31192   -0.52   0.604  -8.20676  4.77571   .303333
 orphdum*|   1.248315      2.9828    0.42   0.676  -4.59787   7.0945   .156667
  natreg |   .2869191      .15424    1.86   0.063  -.015386  .589224   21.6933
natregsq |  -.0010604      .00084   -1.26   0.206  -.002704  .000583   1678.51
wpnoavg3 |  -.0438918      .01511   -2.91   0.004  -.073498 -.014285   86.7467
maxbudg1 |   1.85e-08      .00000    0.73   0.464  -3.1e-08  6.8e-08   9.3e+07
mbudord1 |  -5.66e-09      .00000   -2.54   0.011  -1.0e-08 -1.3e-09   1.7e+09
------------------------------------------------------------------------------
(*) dy/dx is for discrete change of dummy variable from 0 to 1

. streg fsubmits orderent stafcder prevgenx lethal hosp01 hospdisc hhosleng acu
> tediz orphdum natreg natregsq wpnoavg3 maxbudg1 mbudord1,  dist(lognormal) fr
> ailty(invgaussian)

         failure _d:  aprovdum
   analysis time _t:  acttime

Fitting comparison lnormal model:

Fitting constant-only model:

Iteration 0:   log likelihood = -473.31344  (not concave)
Iteration 1:   log likelihood = -408.44906
Iteration 2:   log likelihood = -403.50764
Iteration 3:   log likelihood = -395.72312  (not concave)
Iteration 4:   log likelihood = -393.64638
Iteration 5:   log likelihood = -393.07335
Iteration 6:   log likelihood = -393.02654
Iteration 7:   log likelihood = -393.02537
Iteration 8:   log likelihood = -393.02537
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Fitting full model:

Iteration 0:   log likelihood = -348.45399
Iteration 1:   log likelihood = -335.18048
Iteration 2:   log likelihood = -333.75396
Iteration 3:   log likelihood = -333.62482
Iteration 4:   log likelihood = -333.62445
Iteration 5:   log likelihood = -333.62445

Log-normal regression -- accelerated failure-time form
                      Inverse-Gaussian frailty

No. of subjects =          302                     Number of obs   =       302
No. of failures =          251
Time at risk    =  8797.019171
                                                   LR chi2(14)     =    118.80
Log likelihood  =   -333.62445                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    fsubmits |  -.0182462   .0079004    -2.31   0.021    -.0337306   -.0027618
    orderent |   .0518475    .022981     2.26   0.024     .0068056    .0968894
    stafcder |  -.0014401   .0002045    -7.04   0.000    -.0018409   -.0010392
    prevgenx |   .0021153   .0006647     3.18   0.001     .0008125    .0034181
      lethal |  -.1559954   .1451459    -1.07   0.282    -.4404762    .1284855
      hosp01 |   .3551393   .1610304     2.21   0.027     .0395256     .670753
    hospdisc |   8.56e-08   4.09e-07     0.21   0.834    -7.17e-07    8.88e-07
    hhosleng |  -.0277516   .0132444    -2.10   0.036    -.0537101    -.001793
    acutediz |  -.1147687    .130825    -0.88   0.380    -.3711809    .1416435
     orphdum |   .0768175   .1348068     0.57   0.569     -.187399     .341034
      natreg |   .0131114   .0055705     2.35   0.019     .0021934    .0240293
    natregsq |  -.0000499   .0000306    -1.63   0.103    -.0001099    .0000101
    wpnoavg3 |  -.0017585   .0005152    -3.41   0.001    -.0027683   -.0007488
    maxbudg1 |  -1.41e-10   1.00e-09    -0.14   0.887    -2.10e-09    1.82e-09
    mbudord1 |  -1.73e-10   9.29e-11    -1.86   0.062    -3.55e-10    8.96e-12
       _cons |   4.646264   .2944776    15.78   0.000     4.069099     5.22343
-------------+----------------------------------------------------------------
     /ln_sig |  -.3732675   .0731583    -5.10   0.000    -.5166551     -.22988
     /ln_the |  -1.257177   .5995436    -2.10   0.036     -2.43226   -.0820927
-------------+----------------------------------------------------------------
       sigma |    .688481   .0503681                      .5965125     .794629
       theta |    .284456   .1705438                      .0878381    .9211865
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =     5.52 Prob>=chibar2 = 0.009

. streg fsubmits orderent stafcder prevgenx lethal hosp01 hospdisc hhosleng acu
> tediz orphdum natreg natregsq wpnoavg3 maxbudg1 mbudord1,  dist(lognormal) fr
> ailty(invgaussian) shared(discode)

         failure _d:  aprovdum
   analysis time _t:  acttime

Fitting comparison lnormal model:

Fitting constant-only model:

Iteration 0:   log likelihood = -436.40948  (not concave)
Iteration 1:   log likelihood = -385.08656
Iteration 2:   log likelihood =  -383.2568
Iteration 3:   log likelihood = -383.10174
Iteration 4:   log likelihood = -383.10141
Iteration 5:   log likelihood = -383.10141
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Fitting full model:

Iteration 0:   log likelihood = -344.52403
Iteration 1:   log likelihood = -338.49534
Iteration 2:   log likelihood = -332.21507
Iteration 3:   log likelihood = -331.97517
Iteration 4:   log likelihood = -331.97359
Iteration 5:   log likelihood = -331.97359

Log-normal regression --
        accelerated failure-time form          Number of obs      =       302
        Inverse-Gaussian shared frailty        Number of groups   =        80
Group variable: discode

No. of subjects =          302                 Obs per group: min =         1
No. of failures =          251                                avg =     3.775
Time at risk    =  8797.019171                                max =        47

                                               LR chi2(14)        =    102.26
Log likelihood  =   -331.97359                 Prob > chi2        =    0.0000

------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    fsubmits |  -.0239358   .0077568    -3.09   0.002    -.0391389   -.0087328
    orderent |   .0774477   .0261837     2.96   0.003     .0261286    .1287668
    stafcder |   -.001619   .0002282    -7.09   0.000    -.0020663   -.0011716
    prevgenx |   .0022168   .0008085     2.74   0.006     .0006321    .0038015
      lethal |  -.0525477   .1762369    -0.30   0.766    -.3979657    .2928703
      hosp01 |   .3123014   .2012608     1.55   0.121    -.0821625    .7067653
    hospdisc |   1.39e-07   5.25e-07     0.27   0.791    -8.89e-07    1.17e-06
    hhosleng |  -.0256518   .0155112    -1.65   0.098    -.0560533    .0047497
    acutediz |  -.0823335    .165278    -0.50   0.618    -.4062724    .2416053
     orphdum |   .0886235   .1351298     0.66   0.512    -.1762261    .3534731
      natreg |   .0100047    .007343     1.36   0.173    -.0043872    .0243967
    natregsq |  -.0000336   .0000404    -0.83   0.406    -.0001128    .0000457
    wpnoavg3 |  -.0018965   .0007293    -2.60   0.009    -.0033258   -.0004672
    maxbudg1 |   4.30e-10   1.18e-09     0.36   0.716    -1.88e-09    2.74e-09
    mbudord1 |  -2.55e-10   1.03e-10    -2.48   0.013    -4.57e-10   -5.37e-11
       _cons |   4.845787   .3176469    15.26   0.000     4.223211    5.468364
-------------+----------------------------------------------------------------
     /ln_sig |   -.318684   .0580489    -5.49   0.000    -.4324579   -.2049102
     /ln_the |  -1.183887   .5561645    -2.13   0.033     -2.27395   -.0938249
-------------+----------------------------------------------------------------
       sigma |   .7271052   .0422077                      .6489122    .8147205
       theta |   .3060866   .1702345                      .1029049    .9104422
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =     8.82 Prob>=chibar2 = 0.001

. streg fsubmits orderent stafcder prevgenx lethal deathrt1 hosp01 hospdisc hho
> sleng acutediz orphdum natreg natregsq wpnoavg3 maxbudg1 mbudord1 fmx*,  dist
> (lognormal) frailty(invgaussian) shared(discode)

         failure _d:  aprovdum
   analysis time _t:  acttime
note: fmxAkzoNobel dropped due to collinearity
note: fmxBiogen dropped due to collinearity
note: fmxGenzyme dropped due to collinearity
note: fmxMylan dropped due to collinearity
note: fmxNovoNordisk dropped due to collinearity
note: fmxPierreFabre dropped due to collinearity
note: fmxSankyo dropped due to collinearity
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note: fmxTEVA dropped due to collinearity
note: fmxUCB dropped due to collinearity
note: fmxUpjohn dropped due to collinearity
note: fmxZambon dropped due to collinearity

Fitting comparison lnormal model:

Fitting constant-only model:

Iteration 0:   log likelihood = -432.70794  (not concave)
Iteration 1:   log likelihood = -382.53802
Iteration 2:   log likelihood = -380.90867
Iteration 3:   log likelihood = -380.79745
Iteration 4:   log likelihood = -380.79726
Iteration 5:   log likelihood = -380.79726

Fitting full model:

Iteration 0:   log likelihood = -311.94441
Iteration 1:   log likelihood = -296.32177
Iteration 2:   log likelihood = -295.62647
Iteration 3:   log likelihood = -295.61839
Iteration 4:   log likelihood = -295.61838

Log-normal regression --
         accelerated failure-time form          Number of obs      =       300
         Inverse-Gaussian shared frailty        Number of groups   =        78
Group variable: discode

No. of subjects =          300                  Obs per group: min =         1
No. of failures =          249                                 avg =  3.846154
Time at risk    =  8723.901362                                 max =        47

                                                LR chi2(61)        =    170.36
Log likelihood  =   -295.61838                  Prob > chi2        =    0.0000
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_t	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
fsubmits	-.010014	.014766	-0.68	0.498	-.0389549	.0189269
orderent	.0760317	.0268	2.84	0.005	.0235046	.1285588
stafcder	-.0018563	.0002733	-6.79	0.000	-.0023919	-.0013207
prevgenx	.0030091	.0008401	3.58	0.000	.0013626	.0046555
lethal	-.0929183	.1879658	-0.49	0.621	-.4613245	.2754879
deathrt1	-.2175769	.1734533	-1.25	0.210	-.557539	.1223853
hosp01	.0281186	.2155201	0.13	0.896	-.3942929	.4505302
hospdisc	4.85e-07	5.87e-07	0.83	0.409	-6.66e-07	1.64e-06
hhosleng	-.0105715	.0170451	-0.62	0.535	-.0439792	.0228362
acutediz	-.0271026	.1704686	-0.16	0.874	-.361215	.3070098
orphdum	.2026763	.1357338	1.49	0.135	-.0633571	.4687097
natreg	.0124646	.0077151	1.62	0.106	-.0026567	.027586
natregsq	-.0000348	.000042	-0.83	0.407	-.0001172	.0000475
wpnoavg3	-.0021613	.0007767	-2.78	0.005	-.0036837	-.0006389
maxbudg1	4.72e-10	1.25e-09	0.38	0.705	-1.97e-09	2.92e-09
mbudord1	-2.11e-10	1.04e-10	-2.03	0.042	-4.15e-10	-7.28e-12
fmx3M	-.3339517	.436711	-0.76	0.444	-1.18989	.5219862
fmxAbbott	-.0827565	.2778042	-0.30	0.766	-.6272426	.4617297
fmxAlcon	-.5399909	.341798	-1.58	0.114	-1.209903	.1299208
fmxAllergan	-.1155232	.6718496	-0.17	0.863	-1.432324	1.201278
fmxAmHomeP~s	1.385143	.5181259	2.67	0.008	.3696352	2.400651
fmxAmgen	3.326366	1325.308	0.00	0.998	-2594.23	2600.883
fmxAstaMed~a	-1.797461	.7319925	-2.46	0.014	-3.23214	-.3627816
fmxAstra	-.6496999	.4778963	-1.36	0.174	-1.58636	.2869597

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  fmxAventis |   4.300715   683.0564     0.01   0.995    -1334.465    1343.067
     fmxBayer |  -.3801179   .2738145    -1.39   0.165    -.9167844    .1565485
fmxBoehrin~r |  -.3585447   .2732401    -1.31   0.189    -.8940854     .176996
      fmxBMS |  -.3997816   .2285625    -1.75   0.080    -.8477558    .0481926
fmxCibaGeigy |  -.3916951   .2842291    -1.38   0.168    -.9487738    .1653837
    fmxDuPont |   -.447761   .5228489    -0.86   0.392    -1.472526     .577004
 fmxEliLilly |   .1370128   .3316761     0.41   0.680    -.5130605     .787086
 fmxFujisawa |  -.3221989   .4966092    -0.65   0.516    -1.295535    .6511371
fmxGenentech |   1.961404   4475.346     0.00   1.000    -8769.556    8773.479
    fmxGlaxo |  -.3564371   .4759499    -0.75   0.454    -1.289282    .5764075
fmxGlaxoWe~e |   -.305897   .2621868    -1.17   0.243    -.8197737    .2079796
  fmxHoechst |   -.213285   .2917453    -0.73   0.465    -.7850954    .3585253
fmxJohnson~n |   .0953492   .3055725     0.31   0.755    -.5035619    .6942603
fmxMallinc~t |  -.1140941   .5827091    -0.20   0.845    -1.256183    1.027995
    fmxMerck |  -.5859196   .3255707    -1.80   0.072    -1.224026    .0521872
   fmxSearle |  -1.388384    .640477    -2.17   0.030    -2.643696   -.1330725
 fmxNovartis |   .0918337   .5448028     0.17   0.866    -.9759602    1.159628
      fmxOno |   3.247081   822.7206     0.00   0.997    -1609.256     1615.75
  fmxOrganon |    .332671   .5781898     0.58   0.565    -.8005601    1.465902
   fmxOtsuka |   .9653348   .5513331     1.75   0.080    -.1152582    2.045928
   fmxPfizer |   .0636302   .2608028     0.24   0.807    -.4475339    .5747943
fmxPharmac~n |  -.0038374   .2714834    -0.01   0.989    -.5359352    .5282603
fmxProctor~e |   .2968926   .5306483     0.56   0.576    -.7431589    1.336944
    fmxRhone |  -.3030781   .3961426    -0.77   0.444    -1.079503    .4733471
    fmxRoche |  -.3343196   .2815432    -1.19   0.235    -.8861342     .217495
   fmxSandoz |   .0194247   .3265638     0.06   0.953    -.6206287    .6594781
   fmxSanofi |  -.7980535    .368387    -2.17   0.030    -1.520079   -.0760283
 fmxSchering |  -.1536133   .4293269    -0.36   0.720    -.9950785     .687852
fmxScherin~h |   .6584025   .4137716     1.59   0.112    -.1525748     1.46938
  fmxSearle2 |   .1582765   .4019279     0.39   0.694    -.6294877    .9460407
      fmxSKB |  -.6022997   .2455537    -2.45   0.014    -1.083576   -.1210233
   fmxSolvay |    .825575   .6749438     1.22   0.221    -.4972904     2.14844
   fmxSyntex |   -.143853   .3086678    -0.47   0.641    -.7488307    .4611247
   fmxTakeda |   .1594819   .6898091     0.23   0.817    -1.192519    1.511483
fmxWarnerL~t |   -.632551   .2837307    -2.23   0.026    -1.188653    -.076449
fmxBurroughs |  -.7901745   .3094558    -2.55   0.011    -1.396697   -.1836523
fmxWyethAy~t |   .1017207   .3392463     0.30   0.764    -.5631898    .7666313
   fmxZeneca |  -.4426287   .3773523    -1.17   0.241    -1.182226    .2969682
       _cons |   5.208952     .35387    14.72   0.000      4.51538    5.902525
-------------+----------------------------------------------------------------
     /ln_sig |   -.467874   .0715134    -6.54   0.000    -.6080376   -.3277104
     /ln_the |  -.6991214   .6044243    -1.16   0.247    -1.883771    .4855285
-------------+----------------------------------------------------------------
       sigma |   .6263324   .0447911                      .5444182    .7205717
       theta |   .4970218   .3004121                      .1520157    1.625034
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =     9.51 Prob>=chibar2 = 0.001

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