# Supplementary material

## TEXT FILES

**Instructions to user:** Paste the following text files into Notepad (or other text editor) and save according to the indicated names. These files are necessary to run the following R code and must be saved in the same directory as your code.

### Save as data_table_1.txt

| Study | DI | Age | Weight | Dose | N | Drug |
|---|---|---|---|---|---|---|
| I1 | 37.24928 | 36.79502 | 425.67828 | 1.00000 | 301.00000 | I1 |
| I2 | 20.83333 | 48.69863 | 103.23759 | 1.00000 | 73.00000 | I2 |
| I3 | -20.00000 | 44.50000 | 49.49747 | 1.00000 | 35.00000 | I3 |
| I4 | 17.76266 | 34.90000 | 399.51533 | 1.00000 | 282.50000 | I4 |
| I5 | 28.72671 | 34.90000 | 392.44426 | 1.00000 | 277.50000 | I5 |
| I6 | 12.00000 | 42.96838 | 447.73513 | 1.00000 | 258.50000 | I6 |
| I7 | 17.00000 | 42.63344 | 428.68257 | 1.00000 | 247.50000 | I7 |
| I8 | 23.21429 | 35.50000 | 545.60059 | 1.00000 | 244.00000 | I8 |
| I9 | 21.73038 | 41.00028 | 1190.66830 | 1.00000 | 718.00000 | I9 |
| I10 | 5.58895 | 46.80000 | 1082.53175 | 1.00000 | 625.00000 | I10 |
| I11 | 38.00000 | 36.60356 | 970.96492 | 1.00000 | 1012.00000 | I11 |
| I12 | 26.00000 | 38.00000 | 950.35151 | 1.00000 | 672.00000 | I12 |

### Save as data_table_2.txt

| Study | DI | Age | Weight | Type | N | Drug | Factors |
|---|---|---|---|---|---|---|---|
| A1 | 73.6852475219 | 32.3479820628 | 386.2473300879 | r | 223.00 | A1 | A |
| A2 | 55.1208108605 | 33.0664298401 | 796.2022356161 | r | 563.00 | A2 | A |
| A3 | 60.3937236110 | 35.1216560510 | 888.1261171703 | r | 628.00 | A3 | A |
| D1 | 57.0000000000 | 35.9436893204 | 397.0000000000 | r | 397.00 | D1 | D |
| D2 | 40.6294549591 | 36.2998370451 | 3059.4083231384 | r | 1841.00 | D2 | D |
| DF1 | 21.0000000000 | 37.4977798335 | 733.3878725639 | r | 540.50 | DF1 | DF |
| DF2 | 38.0000000000 | 38.2995110024 | 1108.5622421548 | r | 817.00 | DF2 | DF |
| F1 | 30.0000000000 | 36.8975088968 | 1192.1820330805 | r | 843.00 | F1 | F |
| F2 | 17.0000000000 | 40.3510518934 | 1001.0612848865 | r | 713.00 | F2 | F |
| F3 | 11.9900000000 | 48.5000000000 | 1709.5960415147 | p | 823.00 | F3 | F |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| F4 | 47.1406277608 | 36.3483833718 | 860.0000000000 | r | 860.00 | F4 | F |
| G1 | 12.1951219512 | 34.4494023904 | 354.9676041556 | r | 251.00 | G1 | G |
| G2 | 13.0000000000 | 50.4000000000 | 1619.4675050769 | p | 935.00 | G2 | G |
| G3 | 46.7646964277 | 36.7494764398 | 1036.6481676943 | r | 764.00 | G3 | G |
| G4 | 34.0396567967 | 35.6001486989 | 1899.2888142671 | r | 1343.00 | G4 | G |
| G5 | 7.0000000000 | 37.3417952314 | 721.1760485989 | r | 531.50 | G5 | G |
| G6 | 14.0762708917 | 38.3123772102 | 843.5087432860 | r | 487.00 | G6 | G |
| I1 | 37.2492836676 | 36.7950166113 | 425.6782822743 | r | 301.00 | I1 | I |
| I2 | 20.8333333333 | 48.6986301370 | 103.2375900532 | p | 73.00 | I2 | I |
| I3 | -20.0000000000 | 44.5000000000 | 49.4974746831 | p | 35.00 | I3 | I |
| I4 | 17.7626606198 | 34.9000000000 | 399.5153313704 | r | 282.50 | I4 | I |
| I5 | 28.7267080745 | 34.9000000000 | 392.4442635585 | r | 277.50 | I5 | I |
| I6 | 12.0000000000 | 42.9683788122 | 447.7351337566 | p | 258.50 | I6 | I |
| I7 | 17.0000000000 | 42.6334420881 | 428.6825748733 | p | 247.50 | I7 | I |
| I8 | 23.2142857143 | 35.5000000000 | 545.6005865099 | r | 244.00 | I8 | I |
| I9 | 21.7303822938 | 41.0002785515 | 1190.6682997376 | p | 718.00 | I9 | I |
| I10 | 5.5889530385 | 46.8000000000 | 1082.5317547306 | p | 625.00 | I10 | I |
| I11 | 38.0000000000 | 36.6035573123 | 970.9649220815 | r | 1012.00 | I11 | I |
| I12 | 26.0000000000 | 38.0000000000 | 950.3515139147 | r | 672.00 | I12 | I |
| L1 | 36.0000000000 | 38.7000000000 | 1564.1201999846 | r | 1106.00 | L1 | L |
| L2 | 31.0000000000 | 37.1000000000 | 931.9667376039 | r | 659.00 | L2 | L |
| M1 | 63.6400000000 | 39.9812903226 | 175.3624817343 | rp | 124.00 | M1 | M |
| N1 | 54.0000000000 | 36.0000000000 | 1429.0385189501 | r | 942.00 | N1 | N |
| N2 | 24.0000000000 | 38.9000000000 | 1776.4374795016 | r | 1171.00 | N2 | N |
| N3 | -6.6666666667 | 47.2000000000 | 1203.5430952158 | p | 887.00 | N3 | N |
| O1 | 58.9025459068 | 36.9998781973 | 1113.9897194726 | r | 821.00 | O1 | O |
| O2 | 54.1923860092 | 37.3001197605 | 1132.9858900848 | r | 835.00 | O2 | O |
| O3 | 25.0000000000 | 44.6000000000 | 1234.0700344794 | p | 731.00 | O3 | O |
| R1 | 23.0000000000 | 49.9000000000 | 595.6656356254 | p | 439.00 | R1 | R |
| S1 | 21.0000000000 | 48.0000000000 | 1803.0795184905 | p | 1363.00 | S1 | S |
| T1 | 23.7000000000 | 37.7315068493 | 786.5103704311 | r | 546.50 | T1 | T |
| T2 | 29.8000000000 | 38.0014801110 | 776.4361296388 | r | 539.50 | T2 | T |
| T3 | 5.0000000000 | 37.6259751037 | 746.8718115113 | r | 601.00 | T3 | T |
| T4 | 32.0000000000 | 38.1656663725 | 714.1398730832 | r | 564.00 | T4 | T |

**Save as data_table_3.txt**

| Study | DI | Age | Weight | Type | N | Drug | Efficacy | Factors |
|---|---|---|---|---|---|---|---|---|
| A1 | 73.68524752 | 32.34798206 | 386.2473301 | r | 223 | A1 | 2 | A |
| A2 | 55.12081086 | 33.06642984 | 796.2022356 | r | 563 | A2 | 2 | A |
| A3 | 60.39372361 | 35.12165605 | 888.1261172 | r | 628 | A3 | 2 | A |
| D1 | 57 | 35.94368932 | 397 | r | 397 | D1 | 2 | D |
| D2 | 40.62945496 | 36.29983705 | 3059.408323 | r | 1841 | D2 | 2 | D |
| DF1 | 21 | 37.49777983 | 733.3878726 | r | 540.5 | DF1 | 1 | DF |
| DF2 | 38 | 38.299511 | 1108.562242 | r | 817 | DF2 | 1 | DF |
| F1 | 30 | 36.8975089 | 1192.182033 | r | 843 | F1 | 1 | F |
| F2 | 17 | 40.35105189 | 1001.061285 | r | 713 | F2 | 1 | F |
| F3 | 11.99 | 48.5 | 1709.596042 | p | 823 | F3 | 1 | F |
| F4 | 47.14062776 | 36.34838337 | 860 | r | 860 | F4 | 1 | F |
| G1 | 12.19512195 | 34.44940239 | 354.9676042 | r | 251 | G1 | 1 | G |
| G2 | 13 | 50.4 | 1619.467505 | p | 935 | G2 | 1 | G |
| G3 | 46.76469643 | 36.74947644 | 1036.648168 | r | 764 | G3 | 1 | G |
| G4 | 34.0396568 | 35.6001487 | 1899.288814 | r | 1343 | G4 | 1 | G |
| G5 | 7 | 37.34179523 | 721.1760486 | r | 531.5 | G5 | 1 | G |
| G6 | 14.07627089 | 38.31237721 | 843.5087433 | r | 487 | G6 | 1 | G |
| I1 | 37.24928367 | 36.79501661 | 425.6782823 | r | 301 | I1 | 1 | I |
| I2 | 20.83333333 | 48.69863014 | 103.2375901 | p | 73 | I2 | 1 | I |
| I3 | -20 | 44.5 | 49.49747468 | p | 35 | I3 | 1 | I |
| I4 | 17.76266062 | 34.9 | 399.5153314 | r | 282.5 | I4 | 1 | I |
| I5 | 28.72670807 | 34.9 | 392.4442636 | r | 277.5 | I5 | 1 | I |
| I6 | 12 | 42.96837881 | 447.7351338 | p | 258.5 | I6 | 1 | I |
| I7 | 17 | 42.63344209 | 428.6825749 | p | 247.5 | I7 | 1 | I |
| I8 | 23.21428571 | 35.5 | 545.6005865 | r | 244 | I8 | 1 | I |
| I9 | 21.73038229 | 41.00027855 | 1190.6683 | p | 718 | I9 | 1 | I |
| I10 | 5.588953039 | 46.8 | 1082.531755 | p | 625 | I10 | 1 | I |
| I11 | 38 | 36.60355731 | 970.9649221 | r | 1012 | I11 | 1 | I |
| I12 | 26 | 38 | 950.3515139 | r | 672 | I12 | 1 | I |
| M1 | 63.64 | 39.98129032 | 175.3624817 | rp | 124 | M1 | 2 | M |
| N1 | 54 | 36 | 1429.038519 | r | 942 | N1 | 2 | N |
| N2 | 24 | 38.9 | 1776.43748 | r | 1171 | N2 | 2 | N |
| N3 | -6.666666667 | 47.2 | 1203.543095 | p | 887 | N3 | 2 | N |
| O1 | 58.90254591 | 36.9998782 | 1113.989719 | r | 821 | O1 | 2 | O |
| O2 | 54.19238601 | 37.30011976 | 1132.98589 | r | 835 | O2 | 2 | O |
| O3 | 25 | 44.6 | 1234.070034 | p | 731 | O3 | 2 | O |

|  |  |  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|---|---|
| T1 | 23.7 | 37.73150685 | 786.5103704 | r | 546.5 | T1 | 1 | T |
| T2 | 29.8 | 38.00148011 | 776.4361296 | r | 539.5 | T2 | 1 | T |
| T3 | 5 | 37.6259751 | 746.8718115 | r | 601 | T3 | 1 | T |
| T4 | 32 | 38.16566637 | 714.1398731 | r | 564 | T4 | 1 | T |

**Save as data_table_miss.txt**

| Study | DI | Age | EDSS | Weight | Type | N | Drug | Efficacy | Factors |
|---|---|---|---|---|---|---|---|---|---|
| A1 | 73.68524752 | 32.34798206 | 1.9 | 386.2473301 | r | 223 | A1 | 2 | A |
| A2 | 55.12081086 | 33.06642984 | 2 | 796.2022356 | r | 563 | A2 | 2 | A |
| A3 | 60.39372361 | 35.12165605 | 2.7 | 888.1261172 | r | 628 | A3 | 2 | A |
| D1 | 57 | 35.94368932 | 2.750485437 | 397 | r | 397 | D1 | 2 | D |
| D2 | 40.62945496 | 36.29983705 | 2.5 | 3059.408323 | r | 1841 | D2 | 2 | D |
| DF1 | 21 | 37.49777983 | 2.6 | 733.3878726 | r | 540.5 | DF1 | 1 | DF |
| DF2 | 38 | 38.299511 | 2.4399022 | 1108.562242 | r | 817 | DF2 | 1 | DF |
| F1 | 30 | 36.8975089 | 2.399169632 | 1192.182033 | r | 843 | F1 | 1 | F |
| F2 | 17 | 40.35105189 | 2.4 | 1001.061285 | r | 713 | F2 | 1 | F |
| F3 | 11.99 | 48.5 | 4.67 | 1709.596042 | p | 823 | F3 | 1 | F |
| F4 | 47.14062776 | 36.34838337 | 2.214884527 | 860 | r | 860 | F4 | 1 | F |
| G1 | 12.19512195 | 34.44940239 | 2.599203187 | 354.9676042 | r | 251 | G1 | 1 | G |
| G2 | 13 | 50.4 | 4.9 | 1619.467505 | p | 935 | G2 | 1 | G |
| G3 | 46.76469643 | 36.74947644 | 2.340104712 | 1036.648168 | r | 764 | G3 | 1 | G |
| G4 | 34.0396568 | 35.6001487 | 2.326684015 | 1899.288814 | r | 1343 | G4 | 1 | G |
| G5 | 7 | 37.34179523 | 2.6 | 721.1760486 | r | 531.5 | G5 | 1 | G |
| G6 | 14.07627089 | 38.31237721 | 1.949115914 | 843.5087433 | r | 487 | G6 | 1 | G |
| I1 | 37.24928367 | 36.79501661 | 2.352491694 | 425.6782823 | r | 301 | I1 | 1 | I |
| I2 | 20.83333333 | 48.69863014 | 5.249315068 | 103.2375901 | p | 73 | I2 | 1 | I |
| I3 | -20 | 44.5 | 5.25 | 49.49747468 | p | 35 | I3 | 1 | I |
| I4 | 17.76266062 | 34.9 | 2.466902655 | 399.5153314 | r | 282.5 | I4 | 1 | I |
| I5 | 28.72670807 | 34.9 | 2.466306306 | 392.4442636 | r | 277.5 | I5 | 1 | I |
| I6 | 12 | 42.96837881 | 5.467094703 | 447.7351338 | p | 258.5 | I6 | 1 | I |
| I7 | 17 | 42.63344209 | 5.333442088 | 428.6825749 | p | 247.5 | I7 | 1 | I |
| I8 | 23.21428571 | 35.5 | 2.9 | 545.6005865 | r | 244 | I8 | 1 | I |
| I9 | 21.73038229 | 41.00027855 | 5.149860724 | 1190.6683 | p | 718 | I9 | 1 | I |
| I10 | 5.588953039 | 46.8 | 5.15072 | 1082.531755 | p | 625 | I10 | 1 | I |
| I11 | 38 | 36.60355731 | 2.455177866 | 970.9649221 | r | 1012 | I11 | 1 | I |
| I12 | 26 | 38 | 2.5 | 950.3515139 | r | 672 | I12 | 1 | I |
| L1 | 36 | 38.7 | 2.6 | 1564.1202 | r | 1106 | L1 | NA | L |
| L2 | 31 | 37.1 | 2.5 | 931.9667376 | r | 659 | L2 | NA | L |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| M1 | 63.64 | 39.98129032 | 4.573870968 | 175.3624817 | rp | 124 | M1 | 2 | | M |
| N1 | 54 | 36 | 2.3 | 1429.038519 | r | 942 | N1 | 2 | | N |
| N2 | 24 | 38.9 | 2.4 | 1776.43748 | r | 1171 | N2 | 2 | | N |
| N3 | -6.666666667 | 47.2 | 5.2 | 1203.543095 | p | 887 | N3 | 2 | | N |
| O1 | 58.90254591 | 36.9998782 | 2.804933009 | 1113.989719 | r | 821 | O1 | 2 | | O |
| O2 | 54.19238601 | 37.30011976 | 2.810035928 | 1132.98589 | r | 835 | O2 | 2 | | O |
| O3 | 25 | 44.6 | 4.7 | 1234.070034 | p | 731 | O3 | 2 | | O |
| R1 | 23 | 49.9 | 4.8 | 595.6656356 | p | 439 | R1 | NA | | R |
| S1 | 21 | 48 | 5.4 | 1803.079518 | p | 1363 | S1 | NA | | S |
| T1 | 23.7 | 37.73150685 | 2.68 | 786.5103704 | r | 546.5 | T1 | 1 | | T |
| T2 | 29.8 | 38.00148011 | 2.673358002 | 776.4361296 | r | 539.5 | T2 | 1 | | T |
| T3 | 5 | 37.6259751 | 2.703543568 | 746.8718115 | r | 601 | T3 | 1 | | T |
| T4 | 32 | 38.16566637 | 2.703133274 | 714.1398731 | r | 564 | T4 | 1 | | T |

**Save as data_table_FDA_approve.txt**

| Study | DI | Age | Weight | Type | N | Drug | Efficacy | Factors |
|---|---|---|---|---|---|---|---|---|
| A1 | 73.68524752 | 32.34798206 | 386.2473301 | r | 223 | A1 | 2 | A |
| A2 | 55.12081086 | 33.06642984 | 796.2022356 | r | 563 | A2 | 2 | A |
| A3 | 60.39372361 | 35.12165605 | 888.1261172 | r | 628 | A3 | 2 | A |
| D1 | 57 | 35.94368932 | 397 | r | 397 | D1 | 2 | D |
| D2 | 40.62945496 | 36.29983705 | 3059.408323 | r | 1841 | D2 | 2 | D |
| DF1 | 21 | 37.49777983 | 733.3878726 | r | 540.5 | DF1 | 1 | DF |
| DF2 | 38 | 38.299511 | 1108.562242 | r | 817 | DF2 | 1 | DF |
| F1 | 30 | 36.8975089 | 1192.182033 | r | 843 | F1 | 1 | F |
| F2 | 17 | 40.35105189 | 1001.061285 | r | 713 | F2 | 1 | F |
| F4 | 47.14062776 | 36.34838337 | 860 | r | 860 | F4 | 1 | F |
| G1 | 12.19512195 | 34.44940239 | 354.9676042 | r | 251 | G1 | 1 | G |
| G3 | 46.76469643 | 36.74947644 | 1036.648168 | r | 764 | G3 | 1 | G |
| G4 | 34.0396568 | 35.6001487 | 1899.288814 | r | 1343 | G4 | 1 | G |
| G5 | 7 | 37.34179523 | 721.1760486 | r | 531.5 | G5 | 1 | G |
| G6 | 14.07627089 | 38.31237721 | 843.5087433 | r | 487 | G6 | 1 | G |
| I1 | 37.24928367 | 36.79501661 | 425.6782823 | r | 301 | I1 | 1 | I |
| I4 | 17.76266062 | 34.9 | 399.5153314 | r | 282.5 | I4 | 1 | I |
| I5 | 28.72670807 | 34.9 | 392.4442636 | r | 277.5 | I5 | 1 | I |
| I8 | 23.21428571 | 35.5 | 545.6005865 | r | 244 | I8 | 1 | I |
| I11 | 38 | 36.60355731 | 970.9649221 | r | 1012 | I11 | 1 | I |
| I12 | 26 | 38 | 950.3515139 | r | 672 | I12 | 1 | I |
| M1 | 63.64 | 39.98129032 | 175.3624817 | rp | 124 | M1 | 2 | M |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| N1 | 54 | 36 | 1429.038519 | r | 942 | N1 | 2 | | N |
| N2 | 24 | 38.9 | 1776.43748 | r | 1171 | N2 | 2 | | N |
| O1 | 58.90254591 | 36.9998782 | 1113.989719 | r | 821 | O1 | 2 | | O |
| O2 | 54.19238601 | 37.30011976 | 1132.98589 | r | 835 | O2 | 2 | | O |
| O3 | 25 | 44.6 | 1234.070034 | p | 731 | O3 | 2 | | O |
| T1 | 23.7 | 37.73150685 | 786.5103704 | r | 546.5 | T1 | 1 | | T |
| T2 | 29.8 | 38.00148011 | 776.4361296 | r | 539.5 | T2 | 1 | | T |
| T3 | 5 | 37.6259751 | 746.8718115 | r | 601 | T3 | 1 | | T |
| T4 | 32 | 38.16566637 | 714.1398731 | r | 564 | T4 | 1 | | T |

**R CODE**

**(run in conjunction with above text files)**

```
#----------------------------------------------------------------------------------------------------
# Weighted Regression Analysis for Interferon-Beta, Low Efficacy, and High Efficacy Therapies
# Written by: Ann Marie Weideman (NINDS), Kory R Johnson, Ph.D. (NINDS), Mark Greenwood (MSU)
# Date:  20170512
# Revised: 20170929
# Email: annmarie.weideman@nih.gov, johnsonko@ninds.nih.gov, greenwood.stat@gmail.com
#----------------------------------------------------------------------------------------------------

#install necessary packages (comment out after first run)
#install.packages("stats")
#install.packages("lattice")
#install.packages("effects")
#install.packages("interplot")
#install.packages("grid")

rm(list=ls())
options(object.size=Inf)

library(stats, quietly=T)
library(lattice, quietly=T)
library(effects, quietly=T)
library(interplot,quietly=T)
library(grid, quietly=T)
library(RColorBrewer)
library(ggplot2)

#import data table 1 (interferon-beta trials)
ddd1 <- read.table("data_table_1.txt",header=TRUE,row.names=1)

#import data table 2 (all trials)
ddd2 <- read.table("data_table_2.txt",header=TRUE,row.names=1)
```

```r
#import data table miss (trials with missing efficacy data coded as NA)
ddd.miss<-read.table("data_table_miss.txt",header=TRUE,row.names=1)

#import data table FDA approval (only FDA approved medications for approved MS subtypes)
ddd.approve<-read.table("data_table_FDA_approve.txt",header=TRUE,row.names=1)

#import data table 3 (trials for low/high efficacy plots - excludes Liquinimod, Rituximab, Siponimod)
ddd3 <-read.table("data_table_3.txt",header=TRUE,row.names=1)
ddd3.high <- ddd3[ddd3$Efficacy==2,] #high efficacy trials
ddd3.low <- ddd3[ddd3$Efficacy==1,] #low efficacy trials

#------------------------------------------------------------------------------------------------------
#Define color palettes
#------------------------------------------------------------------------------------------------------

#bubble colors for idebenone trials with transparency (alpha=0.5)
color.idebenone<-adjustcolor(rep("deepskyblue3",12),alpha=0.5)

#bubble colors for all trials with transparency (alpha=0.5)
color.all<-
adjustcolor(c(rep("darkorange",3),rep("red",2),rep("darkmagenta",2),rep("darkslategray1",4),rep("green4",6),
             rep("deepskyblue3",12),rep("lawngreen",2),"tan4",rep("darkred",3),rep("yellow1",3),
             "midnightblue","mistyrose4",rep("peachpuff",4)),alpha=0.5)

#bubble colors for FDA-approved therapies with transparency (alpha=0.5)
color.approve<-
adjustcolor(c(rep("darkorange",3),rep("red",2),rep("darkmagenta",2),rep("darkslategray1",4),rep("green4",6),
                             rep("deepskyblue3",12),"tan4",rep("darkred",3),rep("yellow1",3),
                             rep("peachpuff",4)),alpha=0.5)

#bubble colors for low efficacy therapies with transparency (alpha=0.5)
color.low<-adjustcolor(c(rep("darkmagenta",2),rep("darkslategray1",4),rep("green4",6),
                         rep("deepskyblue3",12),rep("peachpuff",4)),alpha=0.5)

#bubble colors for high efficacy therapies with transparency (alpha=0.5)
color.high<-adjustcolor(c(rep("darkorange",3),rep("red",2),"tan4",
                          rep("darkred",3),rep("yellow1",3)),alpha=0.5)

#legend color scheme for all therapies with transparency (alpha=0.5)
legend.all<-adjustcolor(c("darkorange","red","darkmagenta","darkslategray1","green4",
                            "deepskyblue3","lawngreen","tan4","darkred","yellow1",
                            "midnightblue","mistyrose4","peachpuff"),alpha=0.5)

#legend color scheme for FDA-approved therapies with transparency (alpha=0.5)
legend.approve<-adjustcolor(c("darkorange","red","darkmagenta","darkslategray1","green4",
                          "deepskyblue3","tan4","darkred","yellow1","peachpuff"),alpha=0.5)
```

```
#legend color scheme for high efficacy therapies with transparency (alpha=0.5)
legend.high<-adjustcolor(c("darkorange","red","tan4","darkred","yellow1"),alpha=0.5)

#legend color scheme for low efficacy therapies with transparency (alpha=0.5)
legend.low<-adjustcolor(c("darkmagenta","darkslategray1","green4", "deepskyblue3","peachpuff"),alpha=0.5)


#-------------------------------------------------------------------------------------------------------
#Bubble plot for all interferon-beta trials (Figure 2A)
#-------------------------------------------------------------------------------------------------------

#set for export
jpeg("Plot_IFN_all_fit.jpg", width = 27, height = 31, units = 'in', res = 300)
par(mfrow = c(2, 1),
    oma = c(3, 4, 1, 1),
    mar = c(7, 7, 4, 2),
    mgp = c(5, 2.5, 1))

#create graphing parameters
xrange <- range(c(30,55))
yrange <- range(c(-25,80))
newx.df <- seq(-100,100, length.out=1000)
temp <- data.frame(x=newx.df)
dimnames(temp)[[2]][1] <- "Age"

#fit linear model to data (%Inhibition of Disability Progression (DI) against Age)
ddd1.fit <- lm(DI~Age,data=ddd1,weights=Weight)

#predict confidence intervals
preds.ddd1 <- predict(ddd1.fit,newdata=temp,interval='confidence')

#create plot window for data
plot(xrange, yrange,type = 'n',ylab="",
     xlab="",main="Interferon-beta Trials",cex.axis=2.5,cex.lab=3.25,cex.main=3.5)

#legend for various Interferon Betas inset in graph
legend("topright",
       c("I1, I3, I12 = Avonex","I2, I8, I9, I10 = Betaseron","I11 = Plegridy",
       expression(paste("I4, I6 = Rebif 22", mu,"g")),
       expression(paste("I5, I7 = Rebif 44", mu,"g"))), cex=2.1)

#shared y-axis title
mtext("Inhibition of disability progression (%)",side=2,line=-1,outer=T,cex=3.25)

#draw shaded region of confidence band
polygon(c(rev(newx.df), newx.df), c(rev(preds.ddd1[ ,3]), preds.ddd1[ ,2]), col=rgb(0, 0, 0,0.05), border = NA)
```

```
#add best fit line
abline(coef(ddd1.fit),lty=2)

#draw dashed lines for confidence bands
lines(newx.df, preds.ddd1[ ,3], lty = 'dashed', col = 'black')
lines(newx.df, preds.ddd1[ ,2], lty = 'dashed', col = 'black')

par(new=T)

#draw bubbles using the fact that area = pi*r^2
with(ddd1, symbols(x=Age, y=DI, circles=sqrt(Weight/pi),
                   inches=1.5*sqrt(max(Weight)/max(ddd2$Weight)), ann=F,bg=color.idebenone,
                   xlim = xrange, ylim=yrange, xlab = "", ylab = "", xaxt='n', yaxt='n', pch=16,lwd=1.5))

par(new=T)

#ID labels
text(ddd1$Age,ddd1$DI,dimnames(ddd1)[[1]], cex=2)

box()

#-------------------------------------------------------------
#Bubble plot for simple model (without interaction term)
#used to divide drugs into low and high efficacy categories
#(Figure 2B)
#-------------------------------------------------------------

#fit weighted linear regression (%Inhibition of Disability Progression (DI) against Age)
ddd2.both.fit <- lm(DI~Age,data=ddd2,weights=Weight) #all drugs
ddd.approve.fit <- lm(DI~Age,data=ddd.approve,weights=Weight) #only FDA-approved drugs (subset of all drugs)

#predict confidence intervals
preds.ddd2 <- predict(ddd2.both.fit,newdata=temp,interval='confidence')

#create plot window for data
plot(xrange, yrange,type = 'n',ylab="",
     xlab="Age (years)",main="All Drug Trials",cex.axis=2.5,cex.lab=3.25,cex.main=3.5)

#legend for all drugs inset in graph
legend("topright",
       c("A = Alemtuzumab","D = Daclizumab","DF = Dimethyl Fumarate","F = Fingolimod","G = Glatiramer Acetate",
    "I = Interferon Beta", "L = Laquinimod", "M = Mitoxantrone", "N = Natalizumab","O = Ocrelizumab", "R = Rituximab",
         "S = Siponimod", "T = Teriflunomide"), fill=legend.all, cex=2.1)

#draw shaded region of confidence band
polygon(c(rev(newx.df), newx.df), c(rev(preds.ddd2[ ,3]), preds.ddd2[ ,2]),
```

```
                                       col=rgb(0, 0, 0,0.05), border = NA)

#add best fit line
abline(coef(ddd2.both.fit),lty=2)

#draw dashed lines for confidence bands
lines(newx.df, preds.ddd2[ ,3], lty = 'dashed', col = 'black')
lines(newx.df, preds.ddd2[ ,2], lty = 'dashed', col = 'black')

par(new=T)

#draw bubbles using the fact that area = pi*r^2
with(ddd2, symbols(x=Age, y=DI, circles=sqrt(Weight/pi),
                   inches=1.5, ann=F, bg=color.all,
                   xlim = xrange, ylim=yrange, xlab = "", ylab = "", xaxt='n', yaxt='n',
                   pch=16,lwd=1.5))

par(new=T)

#ID labels
text(ddd2$Age,ddd2$DI,dimnames(ddd2)[[1]], cex=2)

dev.off()

#------------------------------------------------------------------
#Grid for individual regressions (Figure 3)
#------------------------------------------------------------------

tiff("Plot_Grid.tiff", width = 12, height = 8, units = 'in', res = 300,compression = "lzw")

type.f = factor(ddd2$Factors,labels=c("Alemtuzumab", "Daclizumab","Dimethyl Fumarate","Fingolimod",
                                      "Glatiramer Acetate","Interferon-Beta","Laquinimod","Mitoxantrone",
                                      "Natalizumab","Ocrelizumab","Rituximab","Siponimod","Teriflunomide"))
xrange <- range(c(30,55))
yrange <- range(c(-30,80))

#creat grid structure
par(mfrow = c(3, 4))
par(cex = 0.6)
par(mar = c(0.5, 0.5, 0.5, 0.5), oma = c(4, 4, 0.5, 0.5))
par(tcl = -0.25)
par(mgp = c(2, 0.6, 0))

type<-unique(ddd2$Factors)

#iterate over factors to create individual bubble plots
for (i in 1:length(type)) {
```

```r
j<-which(ddd2$Factors==as.character(type[i]))

if(i==12){1}

else{
  if(i %in% c(1,5)){plot(xrange,yrange,xaxt='n',type='n',col.axis = "grey20", cex.axis=1.5)}
  if(i %in% 10:13){plot(xrange,yrange,yaxt='n',type='n',col.axis = "grey20", cex.axis=1.5)}
  if(i==9){plot(xrange,yrange,type='n', col.axis = "grey20", cex.axis=1.5)}
  if(i %in% c(2:4,6:8)){plot(xrange,yrange,axes=F,type='n', col.axis = "grey20", cex.axis=1.5)}

  par(new=T)

  #drug labels
  if(i==7){mtext("Laquinimod/Siponimod", side = 3, line = -1.5, cex = 1.1, col = "black")}
  else{mtext(unique(type.f)[i], side = 3, line = -1.5, cex = 1.1, col = "black")}

  box(col = "grey60")

  par(new=T)

  #plot laquinimod and siponimod together
  if(i==7){
    #draw bubbles for therapy using the fact that area = pi*r^2
    with(ddd2, symbols(x=Age[c(30:31,40)], y=DI[c(30:31,40)], circles=sqrt(Weight[c(30:31,40)]/pi),
                       inches=0.25*sqrt(max(Weight[c(30:31,40)])/max(ddd2$Weight)),
                       ann=F, fg="darkcyan", xlim = xrange, ylim=yrange,
                       xlab = "", ylab = "", xaxt='n',yaxt='n', pch=16,lwd=1.5))
  }

  else{
    #draw bubbles for therapy using the fact that area = pi*r^2
    with(ddd2, symbols(x=Age[j], y=DI[j], circles=sqrt(Weight[j]/pi),
                       inches=0.25*sqrt(max(Weight[j])/max(ddd2$Weight)),
                       ann=F, fg="darkcyan", xlim = xrange, ylim=yrange,
                       xlab = "", ylab = "", xaxt='n',yaxt='n', pch=16,lwd=1.5))
  }

  par(new=T)

  #create band for confidence interval
  polygon(c(rev(newx.df), newx.df), c(rev(unique(preds.ddd2[ ,3])), unique(preds.ddd2[,2])),
          col=rgb(0, 0, 0,0.05), border = NA)

  #add best fit line
  abline(coef(ddd2.both.fit),lty=2)
```

```
    #draw dashed lines for confidence intervals
    lines(newx.df, preds.ddd2[ ,3], lty = 'dashed', col = 'black')
    lines(newx.df, preds.ddd2[ ,2], lty = 'dashed', col = 'black')
  }
}

#label axes
mtext("Age (years)", side = 1, outer = TRUE, cex = 1.3, line = 2.6, col = "grey20")
mtext("Inhibition of Disability Progression (%)", side = 2, outer = TRUE, cex = 1.3, line = 2.3,col = "grey20")

dev.off()

#---------------------------------------------------------------
#Compute weighted standardized residuals (Figure 4 bar charts)
#---------------------------------------------------------------

wres.approve<-c() #vector for residuals of FDA-approved drugs (for approved MS subtypes)
wres.all<-c() #vector for all residuals

#---------------------------------------

#Alemtuzumab (all trials FDA-approved dose in RRMS)
wres.approve$A<-mean(weighted.residuals(ddd.approve.fit)[1:3]/(summary(ddd.approve.fit)$sigma))

#Daclizumab (all trials FDA-approved dose in RRMS)
wres.approve$D<-mean(weighted.residuals(ddd.approve.fit)[4:5]/(summary(ddd.approve.fit)$sigma))

#Dimethyl Fumarate (all trials FDA-approved dose in RRMS)
wres.approve$DF<-mean(weighted.residuals(ddd.approve.fit)[6:7]/(summary(ddd.approve.fit)$sigma))

#Fingolimod (3 trials FDA-approved dose in RRMS)
wres.approve$F<-mean(weighted.residuals(ddd.approve.fit)[8:10]/(summary(ddd.approve.fit)$sigma))

#Glatiramer acetate (5 trials FDA-approved dose in RRMS)
wres.approve$G<-mean(weighted.residuals(ddd.approve.fit)[11:15]/(summary(ddd.approve.fit)$sigma))

#Inteferon-beta (6 trials FDA-approved dose in RRMS)
wres.approve$I<-mean(weighted.residuals(ddd.approve.fit)[16:21]/(summary(ddd.approve.fit)$sigma))

#Mitoxantrone (1 trial FDA-approved dose in SPMS)
wres.approve$M<-mean(weighted.residuals(ddd.approve.fit)[22]/(summary(ddd.approve.fit)$sigma))

#Natalizumab (2 trials FDA-approved dose in RRMS)
wres.approve$N<-mean(weighted.residuals(ddd.approve.fit)[23:24]/(summary(ddd.approve.fit)$sigma))

#Ocrelizumab (all trials FDA-approved dose in RRMS and PPMS)
wres.approve$O<-mean(weighted.residuals(ddd.approve.fit)[25:27]/(summary(ddd.approve.fit)$sigma))
```

```
#Teriflunomide (all trials FDA-approved dose in RRMS)
wres.approve$T<-mean(weighted.residuals(ddd.approve.fit)[28:31]/(summary(ddd.approve.fit)$sigma))

wres.approve.labels<-c("Alemtuzumab","Daclizumab","Dimethyl Fumarate","Fingolimod","Glatiramer Acetate",
                       "Interferon Beta","Mitoxantrone","Natalizumab","Orelizumab","Teriflunomide")
wres.approve.total<-c(wres.approve$A,wres.approve$D,wres.approve$DF,wres.approve$F,wres.approve$G,wres.approve$I,
                      wres.approve$M,wres.approve$N,wres.approve$O,wres.approve$T)

#Color-coded lollipop plot of residuals for approved therapies
tiff("Lollipop_Approve.tiff", width = 18, height = 14, units = 'in', res = 300)

df.approve<-data.frame(x=wres.approve.total,y=wres.approve.labels,color=legend.approve)
df.approve$y<-factor(df.approve$y, levels=df.approve[order(df.approve$x,decreasing=F),]$y)
df.approve$stick<-sapply(df.approve$x,function(x)
  if(x>0.03){round(x,2)-0.095}
  else if(x<0){round(x,2)+0.095}
  else{0})
ggplot(df.approve, aes(x=df.approve$y,y=round(df.approve$x,2),label=round(df.approve$x,2))) +
  theme_bw()+
  geom_segment(aes(y = 0,
                   x = df.approve$y,
                   yend = df.approve$stick,
                   xend = df.approve$y),
               color = "black") +
  geom_point(size=32.3,shape=1,colour="black",show.legend=F)+
  geom_point(colour=df.approve$color,fill=df.approve$color,show.legend=F, size=32,alpha=0.5)  +
  geom_text(color="black",size=9) +
  labs(y="Mean of Standardized Weighted Residuals",x=NULL,title="FDA-Approved Drug Trials")+
  ylim(-1, 1.5) +
  theme(plot.title = element_text(size=36, face="bold"),
        axis.text.x=element_text(colour="black",size=25,margin = margin(t = 10, r = 10, b = 10, l = 10)),
        axis.text.y=element_text(colour="black",size=30,margin = margin(t = 10, r = 10, b = 10, l = 10)),
        axis.title=element_text(size=31))+
  coord_flip()
dev.off()

#----------------------------------------------

#Alemtuzumab (all trials)
wres.all$A<-mean(weighted.residuals(ddd2.both.fit)[1:3]/(summary(ddd2.both.fit)$sigma))

#Daclizumab (all trials)
wres.all$D<-mean(weighted.residuals(ddd2.both.fit)[4:5]/(summary(ddd2.both.fit)$sigma))

#Dimethyl Fumarate (all trials)
wres.all$DF<-mean(weighted.residuals(ddd2.both.fit)[6:7]/(summary(ddd2.both.fit)$sigma))
```

```r
#Fingolimod (all trials)
wres.all$F<-mean(weighted.residuals(ddd2.both.fit)[c(8:11)]/(summary(ddd2.both.fit)$sigma))

#Glatiramer acetate (all trials)
wres.all$G<-mean(weighted.residuals(ddd2.both.fit)[c(12:17)]/(summary(ddd2.both.fit)$sigma))

#Inteferon-beta (all trials)
wres.all$I<-mean(weighted.residuals(ddd2.both.fit)[c(18:29)]/(summary(ddd2.both.fit)$sigma))

#Laquinimod (all trials)
wres.all$L<-mean(weighted.residuals(ddd2.both.fit)[30:31]/(summary(ddd2.both.fit)$sigma))

#Mitoxantrone (all trials)
wres.all$M<-mean(weighted.residuals(ddd2.both.fit)[32]/(summary(ddd2.both.fit)$sigma))

#Natalizumab (all trials)
wres.all$N<-mean(weighted.residuals(ddd2.both.fit)[33:35]/(summary(ddd2.both.fit)$sigma))

#Ocrelizumab (all trials)
wres.all$O<-mean(weighted.residuals(ddd2.both.fit)[36:38]/(summary(ddd2.both.fit)$sigma))

#Rituximab (all trials)
wres.all$R<-mean(weighted.residuals(ddd2.both.fit)[39]/(summary(ddd2.both.fit)$sigma))

#Siponimod (all trials)
wres.all$S<-mean(weighted.residuals(ddd2.both.fit)[40]/(summary(ddd2.both.fit)$sigma))

#Teriflunomide (all trials)
wres.all$T<-mean(weighted.residuals(ddd2.both.fit)[41:44]/(summary(ddd2.both.fit)$sigma))

wres.all.labels<-c("Alemtuzumab","Daclizumab","Dimethyl Fumarate","Fingolimod","Glatiramer Acetate",
                    "Interferon Beta","Laquinimod","Mitoxantrone","Natalizumab","Orelizumab",
                   "Rituximab","Siponimod","Teriflunomide")
wres.all.total<-c(wres.all$A,wres.all$D,wres.all$DF,wres.all$F,wres.all$G,wres.all$I,wres.all$L,
                  wres.all$M,wres.all$N,wres.all$O,wres.all$R,wres.all$S,wres.all$T)

#Color-coded lollipop plot of residuals for all therapies
tiff("Lollipop_All.tiff", width = 18, height = 14, units = 'in', res = 300)

df.all<-data.frame(x=wres.all.total,y=wres.all.labels,color=legend.all)
df.all$y<-factor(df.all$y, levels=df.all[order(df.all$x,decreasing=F),]$y)
df.all$stick<-sapply(df.all$x,function(x)
  if(x>0.03){round(x,2)-0.095}
  else if(x<0){round(x,2)+0.095}
  else{0})
ggplot(df.all, aes(x=df.all$y,y=round(df.all$x,2),label=round(df.all$x,2))) +
```

```
  theme_bw()+
  geom_segment(aes(y = 0,
                   x = df.all$y,
                   yend = df.all$stick,
                   xend = df.all$y),
               color = "black") +
  geom_point(size=32.3,shape=1,colour="black",show.legend=F)+
  geom_point(colour=df.all$color,fill=df.all$color,show.legend=F, size=32,alpha=0.5)  +
  geom_text(color="black",size=9) +
  labs(y="Mean of Standardized Weighted Residuals",x=NULL,title="All Drug Trials")+
  ylim(-1, 1.5) +
  theme(plot.title = element_text(size=36, face="bold"),
        axis.text.x=element_text(colour="black",size=25,margin = margin(t = 10, r = 10, b = 10, l = 10)),
        axis.text.y=element_text(colour="black",size=30,margin = margin(t = 10, r = 10, b = 10, l = 10)),
        axis.title=element_text(size=31))+
  coord_flip()
dev.off()

#----------------------------------------------------------------
#Fit model with interaction term
#----------------------------------------------------------------

#convert to factor
ddd.miss$Efficacy<-as.factor(ddd.miss$Efficacy)

#fit weighted regression with interaction term via step-down procedure
ddd.miss.fitv0<-lm(DI~Age*Efficacy*EDSS,data=ddd.miss,weights=Weight,na.action=na.exclude); summary(ddd.miss.fitv0)
ddd.miss.fitv1<-lm(DI~Age*Efficacy+Age*EDSS+EDSS*Efficacy,data=ddd.miss,weights=Weight,na.action=na.exclude);
summary(ddd.miss.fitv1)
ddd.miss.fitv2<-lm(DI~Age*Efficacy+EDSS*Efficacy,data=ddd.miss,weights=Weight,na.action=na.exclude);
summary(ddd.miss.fitv2)
ddd.miss.fitv3<-lm(DI~Age*Efficacy+EDSS,data=ddd.miss,weights=Weight,na.action=na.exclude); summary(ddd.miss.fitv3)
ddd.miss.fit<-lm(DI~Age*Efficacy,data=ddd.miss,weights=Weight,na.action=na.exclude)

#check model fit
summary(ddd.miss.fit)
confint(ddd.miss.fit)
par(mfrow=c(2,2))
plot(ddd.miss.fit)
par(mfrow=c(1,1))

#residuals versus fitted
plot(residuals(ddd.miss.fit)~ddd.miss$Age,col=ddd.miss$Efficacy,pch=16+as.numeric(ddd.miss$Efficacy))

#effect plot
plot(effect("Age*Efficacy",mod=ddd.miss.fit,xlevels=list(Efficacy=c(1,2))))
```

```
#---------------------------------------------------------------------
#Bubble Plot for model with interaction term (Figure 4C)
#---------------------------------------------------------------------
#set for export
tiff("Plot_both_high_fit.tiff", width = 19, height = 25, units = 'in', res = 300)
par(mfrow = c(2, 1),
    oma = c(3, 4, 1, 1),
    mar = c(7, 7, 3, 2),
    mgp = c(5, 2.5, 1))

#create plot window for data
plot(xrange, yrange,type = 'n',ylab="Inhibition of disability progression (%)",
     xlab="",main="FDA-Approved Drug Trials",cex.axis=2,cex.lab=2.75,cex.main=3)

#legend for FDA-approved therapies (inset in graph)
legend("topright",
       c("A = Alemtuzumab","D = Daclizumab","DF = Dimethyl Fumarate","F = Fingolimod","G = Glatiramer Acetate",
         "I = Interferon Beta","M = Mitoxantrone", "N = Natalizumab","O = Ocrelizumab",
         "T = Teriflunomide"), fill=legend.approve, cex=2)

lines(newx.df, predict(ddd.miss.fit, data.frame(Age = newx.df,
                                                Efficacy = factor(rep(1, length(newx.df))))),lty=2)

lines(newx.df, predict(ddd.miss.fit, data.frame(Age = newx.df,
                                                Efficacy = factor(rep(2, length(newx.df))))),lty=2)

par(new=T)

#predict confidence intervals
preds.ddd.miss1 <- predict(ddd.miss.fit,data.frame(Age = newx.df,
                                                   Efficacy = factor(rep(1, length(newx.df)))),interval='confidence')
preds.ddd.miss2 <- predict(ddd.miss.fit,data.frame(Age = newx.df,
                                                   Efficacy = factor(rep(2, length(newx.df)))),interval='confidence')

#create band for confidence interval
polygon(c(rev(newx.df), newx.df), c(rev(unique(preds.ddd.miss1[ ,3])), unique(preds.ddd.miss1[,2])),
        col=rgb(0, 0, 0,0.05), border = NA)

polygon(c(rev(newx.df), newx.df), c(rev(unique(preds.ddd.miss2[ ,3])), unique(preds.ddd.miss2[,2])),
        col=rgb(0, 0, 0,0.05), border = NA)

#draw dashed lines for confidence intervals
lines(newx.df, preds.ddd.miss1[ ,3], lty = 'dashed', col = 'black')
lines(newx.df, preds.ddd.miss1[ ,2], lty = 'dashed', col = 'black')
lines(newx.df, preds.ddd.miss2[ ,3], lty = 'dashed', col = 'black')
lines(newx.df, preds.ddd.miss2[ ,2], lty = 'dashed', col = 'black')
```

```r
par(new=T)

with(ddd3,symbols(x=Age, y=DI, circles=sqrt(Weight/pi),
                  inches=1.3, ann=F,
                  bg=color.approve,xlim = xrange, ylim=yrange, xlab = "", ylab = "", xaxt='n',yaxt='n',lwd=1.5))

par(new=T)

#ID bubbles
text(ddd3$Age,ddd3$DI,dimnames(ddd3)[[1]],cex=1.7)

box()

#-----------------------------------------------------------------------------------------------------
#Bubble plot for trials of high efficacy therapies (Figure 4E)
#-----------------------------------------------------------------------------------------------------

#create graphing parameters
xrange <- range(c(30,55))
yrange <- range(c(-25,80))
newx.df <- seq(-100,100, length.out=500)
temp <- data.frame(newx.df)
dimnames(temp)[[2]][1] <- "Age"

ddd3.high.fit<-lm(DI~Age,data=ddd3.high,weights=Weight)

#predict 95% confidence intervals
preds.ddd3.high <- predict(ddd3.high.fit,newdata=temp,interval='confidence')

#create plot window for data
plot(xrange, yrange,type = 'n',ylab="Inhibition of disability progression (%)",
     xlab="Age (years)",main="High Efficacy Drug Trials",cex.axis=2,cex.lab=2.75,cex.main=3)

#legend for high efficacy therapies (inset in graph)
legend("topright",
       c("A = Alemtuzumab","D = Daclizumab","M = Mitoxantrone", "N = Natalizumab","O = Ocrelizumab"),
       fill=legend.high, cex=2)

#draw shaded region of confidence band
polygon(c(rev(newx.df), newx.df), c(rev(preds.ddd3.high[ ,3]), preds.ddd3.high[ ,2]), col=rgb(0, 0, 0,0.05), border =
NA)

#add best fit line
abline(coef(ddd3.high.fit),lty=2)

#draw dashed lines for confidence intervals
lines(newx.df, preds.ddd3.high[ ,3], lty = 'dashed', col = 'black')
```

```r
lines(newx.df, preds.ddd3.high[ ,2], lty = 'dashed', col = 'black')

par(new=T)

#draw high efficacy bubbles using the fact that area = pi*r^2
with(ddd3.high,symbols(x=Age, y=DI, circles=sqrt(Weight/pi),
                       inches=1.3, ann=F,bg=color.high,xlim = xrange, ylim=yrange, xlab = "",
                       ylab = "", xaxt='n',yaxt='n',lwd=1.5))

par(new=T)

#ID bubbles
text(ddd3.high$Age,ddd3.high$DI,dimnames(ddd3.high)[[1]],cex=1.7)

dev.off()

#----------------------------------------------------------------------------------------------------
#Bubble plot for trials of low efficacy therapies (Figure 4D)
#----------------------------------------------------------------------------------------------------

#set for export
tiff("Plot_low_ttest_fit.tiff", width = 19, height = 25, units = 'in', res = 300)
par(mfrow = c(2, 1),
    oma = c(3, 4, 1, 1),
    mar = c(7, 7, 3, 2),
    mgp = c(5, 2.5, 1))

#create graphing parameters
xrange <- range(c(30,55))
yrange <- range(c(-25,80))
newx.df <- seq(-100,100, length.out=500)
temp <- data.frame(newx.df)
dimnames(temp)[[2]][1] <- "Age"

#add best fit lines
ddd3.low.fit<-lm(DI~Age,data=ddd3.low,weights=Weight)

#predict 95% confidence intervals
preds.ddd3.low <- predict(ddd3.low.fit,newdata=temp,interval='confidence')

#create plot window for data
plot(xrange, yrange,type = 'n',ylab="Inhibition of disability progression (%)",
     xlab="",main="Low Efficacy Drug Trials",cex.axis=2,cex.lab=2.75,cex.main=3)

#legend for low efficacy therapies (inset in graph)
legend("topright", c("DF = Dimethyl Fumarate","F = Fingolimod","G = Glatiramer Acetate",
                     "I = Interferon Beta", "T = Teriflunomide"), fill=legend.low, cex=2)
```

```r
#draw shaded region of confidence band
polygon(c(rev(newx.df), newx.df), c(rev(preds.ddd3.low[ ,3]), preds.ddd3.low[ ,2]), col=rgb(0, 0, 0,0.05), border = NA)

#add best fit line
abline(coef(ddd3.low.fit),lty=2)

#draw dashed lines for confidence intervals
lines(newx.df, preds.ddd3.low[ ,3], lty = 'dashed', col = 'black')
lines(newx.df, preds.ddd3.low[ ,2], lty = 'dashed', col = 'black')

par(new=T)

#draw low efficacy bubbles using the fact that area = pi*r^2
with(ddd3.low,symbols(x=Age, y=DI, circles=sqrt(Weight/pi),
                      inches=1.3*sqrt(max(Weight)/max(ddd2$Weight)), ann=F,
                      bg=color.low,xlim = xrange, ylim=yrange, xlab = "", ylab = "", xaxt='n',yaxt='n',lwd=1.5))

par(new=T)

#ID bubbles
text(ddd3.low$Age,ddd3.low$DI,dimnames(ddd3.low)[[1]],cex=1.7)

box()

#-------------------------------------------------------------------
#t-test for difference in means (Figure 4F)
#-------------------------------------------------------------------

#create graphing parameters
xrange <- range(c(30,55))
yrange <- range(c(-50,50))
newx.df <- seq(-100,100, length.out=500)
temp <- data.frame(x=newx.df)
dimnames(temp)[[2]][1] <- "Age"

#compute differences in means between high and low efficacy data
ddd.miss.fake<-data.frame(Age=rep(seq(from=25,to=60,length.out=100),1),Efficacy=factor(rep(c(2),each=100)))
newx<-rbind(model.matrix(ddd.miss.fit)[1:30,],model.matrix(ddd.miss.fit)[1:30,],
            model.matrix(ddd.miss.fit)[1:30,],model.matrix(ddd.miss.fit)[1:10,])
newx[,1:2]<-0
newx[,3]<-1
newx[,4]<-ddd.miss.fake$Age
SEs<-sqrt(diag(newx%*%vcov(ddd.miss.fit)%*%t(newx)))
estdiff<-newx%*%ddd.miss.fit$coefficients

plot(xrange, yrange,type = 'n',ylab="Difference in Means",
```

```
     xlab="Age (years)",main="Difference between High & Low Efficacy Drugs",cex.axis=2,cex.lab=2.75,cex.main=3)

#add best fit line to data
abline(lm(estdiff~ddd.miss.fake$Age),lty=1,lwd=2)

#compute 95% confidence interval estimates (difference in means, t-test)
SEs<-sqrt(diag(newx%*%vcov(ddd.miss.fit)%*%t(newx)))
lines(estdiff-qt(.975,df=33)*SEs~ddd.miss.fake$Age,lwd=2,lty=2,col="red")
lines(estdiff+qt(.975,df=33)*SEs~ddd.miss.fake$Age,lwd=2,lty=2,col="red")
abline(h=0,col="gray15",lwd=2)
abline(v=40.5,col="gray15",lwd=2,lty=2)

dev.off()
```