Supplementary Online Content

Goyal A, Schibler T, Alhanti B, et al. Assessment of North American clinical research site performance during the start-up of large cardiovascular clinical trials. *JAMA Netw Open.* 2021;4(7):e2117963. doi:10.1001/jamanetworkopen.2021.17963

**eFigure 1.** Regulatory Approval Time by Trial

**eFigure 2.** Contract Execution Time by Trial

**eFigure 3.** Activation Time by Trial

**eFigure 4.** Enrollment of First Participant Time by Trial

**eFigure 5.** Overall Start-Up Time by Trial

**eFigure 6.** Side-by-Side Boxplots of Regulatory Approval and Contract Execution by 2004-2007 vs 2008-2012 Trials

**eFigure 7.** Side-by-Side Boxplots of Regulatory Approval and Contract Execution by Trial

**eTable 1.** Milestone Pacing Site Activation

**eTable 2.** Milestone Pacing to Site Activation for Individual Trials

**eTable 3.** Time to Regulatory Approval for Individual Trials by IRB Type

**eTable 4.** Time to Overall Start-Up for Individual Trials by IRB Type

This supplementary material has been provided by the authors to give readers additional information about their work.

© 2021 Goyal A et al. *JAMA Network Open.*
eFigure 1. Regulatory Approval Time by Trial

Caption: The time to regulatory approval for each trial represented by the percent of sites completing the milestone at a given time in days.
eFigure 2. Contract Execution Time by Trial

Caption: The time to contract execution for each trial represented by the percent of sites completing the milestone at a given time in days.
**eFigure 3. Activation Time by Trial**

The activation time for each trial represented by the percent of sites completing the milestone at a given time in days.

© 2021 Goyal A et al. *JAMA Network Open.*
Caption: The time to enrollment of the first participant for each trial represented by the percent of sites completing the milestone at a given time in days.
**eFigure 5. Overall Start-Up Time by Trial**

![Overall Start-Up Time by Trial](image)

Caption: The overall start-up time for each trial represented by the percent of sites completing the milestone at a given time in days.
Caption: The boxplots show the days required to reach both regulatory approval and contract execution stratified by early trials from 2004-2007 (APEX-AMI, IMPROVE-IT, ROCKET-AF, ASCEND-AF, & TRACER) and contemporary trials from 2008-2012 (TECOS, EXSCEL, ODYSSEY, & EUCLID).
eFigure 7. Side-by-Side Boxplots of Regulatory Approval and Contract Execution by Trial

| Trial name | Regulatory Approval | Contract Execution | Regulatory Approval | Contract Execution | Regulatory Approval | Contract Execution |
|------------|---------------------|--------------------|---------------------|--------------------|---------------------|--------------------|
| APEXAMI    | 102                 | 146                | 96                  | 169                | 110.5               | 231.5              |
| IMPROVEIT  | 87                  | 131                | 136.5               | 211.5              | 69                  | 112                |
| ROCKET-AF  | 197                 | 195                | 211.5               | 231.5              | 47                  | 78                 |
| ASCEND_HF  | 110.5               | 171.5              | 113                 | 169                | 48                  | 96.5               |
| TRACER     | 124                 | 189                | 169                 | 666                | 54                  | 119                |
| TECOS      | 246                 | 254                | 254                 | 902                | 169                 | 284                |
| EXSCEL     | 46                  | 104                | 48                  | 112                | 83                  | 118.5              |
| ODYSSEY_OC | 54                  | 99                 | 56                  | 193                | 100.5               | 172                |
| EUCLID     | 159                 | 189                | 189                 | 275                | 122                 |                    |

Caption: The boxplots show the days required to reach both regulatory approval and contract execution stratified by individual trial.
**eTable 1. Milestone Pacing Site Activation**

| Milestone                                                                 | All Trials | 2004-2007 Trials | 2008-2012 Trials | P-value‡ |
|---------------------------------------------------------------------------|------------|------------------|------------------|----------|
| Contract Complete First, (% of sites)                                     | 49.6%      | 52.0%            | 46.6%            | 0.02     |
| Regulatory Approval first; Subsequent Time to Contract Execution (days)   | 46 (13, 155) | 60 (20, 210)    | 33 (8, 111)      | <0.001   |
| Contract Execution first; Subsequent Time to Regulatory Approval (days)   | 30 (12, 63) | 33 (14, 63)      | 27 (8, 61)       | 0.03     |

Continuous variables are described using median (25th, 75th percentile). Categorical variables are described using frequency (%). ²2004-2007 trials: APEX-AMI, IMPROVE-IT, ROCKET-AF, ASCEND-AF, & TRACER; ²2008-2012 trials: TECOS, EXSCEL, ODYSSEY, & EUCLID; ³P-value describes difference between 2004-2007 and 2008-2012 trials.

**eTable 2. Milestone Pacing to Site Activation for Individual Trials**

| Trial         | Contract Execution First, (% of sites) | Regulatory Approval First; Subsequent Time to Contract Execution (days) | Contract Execution First; Subsequent Time to Regulatory Approval (days) |
|---------------|----------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| APEX-AMI      | 55.6%                                  | 20 (6, 46)                                                               | 26 (7, 47)                                                               |
| IMPROVE-IT    | 45.1%                                  | 51 (18, 83)                                                              | 28 (12, 51)                                                              |
| ROCKET-AF     | 76.3%                                  | 29 (8, 63)                                                               | 44 (20, 74)                                                              |
| ASCEND-HF     | 55.2%                                  | 48 (18, 100)                                                             | 29 (13, 58)                                                              |
| TRACER        | 25.2%                                  | 642 (377, 758)                                                          | 40 (15, 84)                                                              |
| TECOS         | 47.5%                                  | 35 (6, 777)                                                              | 24 (8, 54)                                                               |
| EXSCEL        | 49.5%                                  | 34 (5, 99)                                                               | 30 (9, 71)                                                               |
| ODYSSEY       | 48.0%                                  | 22 (7, 69)                                                               | 29 (9, 57)                                                               |
| EUCLID        | 39.5%                                  | 54 (23, 150)                                                             | 25 (8, 55)                                                               |

Continuous variables are described using median (25th, 75th percentile). Categorical variables are described using frequency (%).
### eTable 3. Time to Regulatory Approval for Individual Trials by IRB Type

| Trial       | IRB Type | Number of Sites, n | Time to Regulatory Approval, days |
|-------------|----------|--------------------|-----------------------------------|
|             |          |                    |                                    |
| APEX-AMI    | All sites| 207                | 146 (102, 197)                    |
|             | Local    | 207 (100%)         | 146 (102, 197)                    |
|            |          |                    |                                    |
| IMPROVE-IT  | All sites| 252                | 137 (96, 212)                     |
|             | Local    | 252 (100%)         | 137 (96, 212)                     |
|            |          |                    |                                    |
| ROCKET-AF   | All sites| 283                | 112 (69, 189)                     |
|             | Central  | 185 (65.4%)        | 84 (56, 130)                      |
|             | Local    | 89 (31.4%)         | 194 (140, 286)                    |
|             | Missing  | 9 (3.2%)           | 285 (156, 407)                    |
|            |          |                    |                                    |
| ASCEND_HF   | All sites| 280                | 172 (111, 240)                    |
|             | Central  | 15 (5.4%)          | 172 (109, 265)                    |
|             | Local    | 90 (32.1%)         | 176 (127, 262)                    |
|             | Missing  | 175 (62.5%)        | 167 (107, 236)                    |
|            |          |                    |                                    |
| TRACER      | All sites| 286                | 169 (113, 254)                    |
|             | Central  | 58 (20.3%)         | 134 (71, 216)                     |
|             | Local    | 225 (78.6%)        | 183 (121, 258)                    |
|             | Missing  | 3 (1.0%)           | 192 (90, 301)                     |
|            |          |                    |                                    |
| TECOS       | All sites| 210                | 97 (48, 169)                      |
|             | Central  | 97 (46.2%)         | 55 (41, 86)                       |
|             | Local    | 94 (44.8%)         | 159 (100, 261)                    |
|             | Missing  | 19 (9.0%)          | 102 (26, 193)                     |
|            |          |                    |                                    |
| EXSCEL      | All sites| 207                | 104 (46, 159)                     |
|             | Central  | 145 (70.0%)        | 65 (38, 117)                      |
|             | Local    | 50 (24.2%)         | 194 (145, 332)                    |
|             | Missing  | 12 (5.8%)          | 132 (62, 220)                     |
|            |          |                    |                                    |
| ODYSSEY     | All sites| 330                | 100 (48, 189)                     |
|             | Central  | 193 (58.5%)        | 58 (35, 102)                      |
|             | Local    | 137 (41.5%)        | 190 (130, 276)                    |
|            |          |                    |                                    |
| EUCLID      | All sites| 170                | 119 (83, 209)                     |
|             | Central  | 105 (61.8%)        | 102 (76, 124)                     |
|             | Local    | 65 (38.2%)         | 209 (121, 252)                    |

Continuous variables are described using median (25th, 75th percentile). Categorical variables are described using frequency (%). IRB = institutional review board.
### eTable 4. Time to Overall Start-Up for Individual Trials by IRB Type

| Trial          | IRB Type | Number of Sites, n | Time to Overall Start-up, days |
|----------------|----------|--------------------|---------------------------------|
| APEX-AMI       | All sites| 165                | 249 (175, 316)                  |
|                | Local    | 165 (100%)         | 249 (175, 316)                  |
| IMPROVE-IT     | All sites| 193                | 265 (194, 344)                  |
|                | Local    | 193 (100%)         | 265 (194, 344)                  |
| ROCKET-AF      | All sites| 196                | 211 (142, 328)                  |
|                | Central  | 141 (71.9%)        | 181 (125, 246)                  |
|                | Local    | 54 (27.6%)         | 332 (253, 412)                  |
|                | Missing  | 1 (0.5%)           | 602 (602, 602)                  |
| ASCEND_HF      | All sites| 212                | 298 (230, 378)                  |
|                | Central  | 15 (7.1%)          | 324 (268, 351)                  |
|                | Local    | 89 (42.0%)         | 308 (226, 386)                  |
|                | Missing  | 108 (50.9%)        | 289 (230, 380)                  |
| TRACER         | All sites| 248                | 290 (203, 413)                  |
|                | Central  | 52 (21.0%)         | 258 (197, 370)                  |
|                | Local    | 196 (79.0%)        | 299 (207, 423)                  |
| TECOS          | All sites| 184                | 194 (128, 273)                  |
|                | Central IRB | 78 (42.4%)    | 145 (98, 196)                  |
|                | Local IRB | 92 (50.0%)        | 232 (168, 345)                  |
|                | Missing IRB | 14 (7.6%)     | 205 (115, 262)                  |
| EXSCEL         | All sites| 187                | 183 (137, 246)                  |
|                | Central IRB | 137 (73.3%)   | 162 (129, 200)                  |
|                | Local IRB | 47 (25.1%)        | 264 (207, 439)                  |
|                | Missing IRB | 3 (1.6%)       | 222 (215, 451)                  |
| ODYSSEY        | All sites| 285                | 292 (203, 405)                  |
|                | Central IRB | 169 (59.3%)   | 249 (179, 336)                  |
|                | Local IRB | 116 (40.7%)       | 359 (275, 508)                  |
| EUCLID         | All sites| 142                | 280 (223, 343)                  |
|                | Central IRB | 98 (62.7%)      | 252 (198, 301)                  |
|                | Local IRB | 53 (37.3%)        | 329 (278, 400)                  |

Continuous variables are described using median (25th, 75th percentile). Categorical variables are described using frequency (%). IRB = institutional review board.