Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.
eMethods 1: Expert Survey Questionnaire

Instructions:

The questions in this survey involve the costs and time required to conduct randomized clinical trials (RCTs). The responses will be used to compare the efficiency of different approaches in conducting clinical trials: 1) 2-arm trials; 2) multi-arm trials; and 3) platform trials.

First, we are considering traditional 2-arm trials with one experimental intervention arm being compared to the control arm. Second, we consider multi-arm trials, where there are two or more experimental intervention arms being compared against the control arm. Lastly, we are considering platform trials, a relatively newer type of randomized clinical trial designs that allow simultaneous comparison of multiple interventions against a common control using a pre-specified interim analyses plan. This single overarching protocol called a master (or core) protocol dictates how new interventions are introduced after the trial is initiated, thus allowing for multiple interventions to be evaluated in a perpetual manner.

This survey will begin by asking general questions about your area of expertise, current employment sector, and role in clinical trial related research. The part of the questionnaire regarding costs is broken into three parts of 1) Trial setup; 2) Trial conduct; and 3) Trial analyses.

This survey is not intended to be exhaustive. It is intended to identify key costing items that will allow us to compare different clinical trial evaluation approaches to each other.

Please try to answer all questions so that we can compare the costs of different clinical trials fairly.

General information:

1) Please indicate the country of your residence (e.g. US, UK)?

2) Please indicate your PRIMARY role in clinical trials related research
   a) Clinical investigator
   b) Health economist
   c) Journal editor
   d) Regulatory assessor
   e) Research ethicist
   f) Research funding board/panel member
   g) Trial manager
   h) Trial methodologist
   i) Other: Please specify ______

3) Please indicate your CURRENT employment sector. Select all that apply.
   a) Public sector
   b) Industry
   c) Philanthropy
   d) Regulatory agency
   e) Other: Please specify_____

4) Please indicate therapeutic area(s) that you have experience in. Select ALL that apply
   • Cardiology
   • Dermatology
   • Gastroenterology
   • Hematology
• Immunology
• Infectious diseases
• Metabolism and endocrinology
• Neurology
• Oncology
• Psychiatry
• Rheumatology
• Urology
• Other: Please specify ______

5) Please indicate your experience in clinical trial research. Select ALL that apply
   a) Trial protocol development
   b) Trial approval submission (e.g. ethics and regulatory approval submission)
   c) Trial database development and/or management
   d) Trial operation planning
   e) Trial conduct and reporting
   f) Trial budgeting
   g) Ethics and/or regulatory assessment
   h) Statistical analyses and/or data safety monitoring board (DSMB)

Trial set-up:

The following questions are aimed to gather broad estimates across all therapeutic areas and for most situations.

Time required to develop a trial protocol (in months)
1) In your opinion, what is the time required to develop a study trial protocol for the following clinical trials?

|                     | 2-arm trial | Multi-arm trial | Platform trial |
|---------------------|-------------|-----------------|----------------|
| Average (months)    |             |                 |                |
| Minimum (months)    |             |                 |                |
| Maximum (months)    |             |                 |                |

Cost required to develop a trial protocol (in 2021 USD)
2) In your opinion, what is the cost required to develop a study trial protocol for the following clinical trials?

|                     | 2-arm trial | Multi-arm trial | Platform trial |
|---------------------|-------------|-----------------|----------------|
| Average ($)         |             |                 |                |
| Minimum ($)         |             |                 |                |
| Maximum ($)         |             |                 |                |

Time required to obtain study approval (in months)
3) In your opinion, what is the time required to obtain study approvals for the following clinical trials?

|                     | 2-arm trial | Multi-arm trial | Platform trial |
|---------------------|-------------|-----------------|----------------|
| Average (months)    |             |                 |                |
| Minimum (months)    |             |                 |                |
| Maximum (months)    |             |                 |                |

Cost required to obtain study approval (in 2021 USD)
4) In your opinion, what is the cost required to obtain study approvals for the following clinical trials?

|                      | 2-arm trial | Multi-arm trial | Platform trial |
|----------------------|-------------|-----------------|----------------|
| Average ($)          |             |                 |                |
| Minimum ($)          |             |                 |                |
| Maximum ($)          |             |                 |                |

**Time required for database development (in months)**

5) In your opinion, what is the time required to set up a database for the following clinical trials?

|                      | 2-arm trial | Multi-arm trial | Platform trial |
|----------------------|-------------|-----------------|----------------|
| Average (months)     |             |                 |                |
| Minimum (months)     |             |                 |                |
| Maximum (months)     |             |                 |                |

**Cost required for database development (in 2021 USD)**

6) In your opinion, what is the cost required to set up a database for the following clinical trials?

|                      | 2-arm trial | Multi-arm trial | Platform trial |
|----------------------|-------------|-----------------|----------------|
| Average ($)          |             |                 |                |
| Minimum ($)          |             |                 |                |
| Maximum ($)          |             |                 |                |

**Cost required to set up clinical trial sites (in 2021 USD)**

7) In your opinion, what is the cost required to set up a single clinical trial site for a clinical trial?

|                      | Clinical trial |
|----------------------|----------------|
| Average ($)          |                |
| Minimum ($)          |                |
| Maximum ($)          |                |
**Trial conduct:**

Please estimate the cost required for conducting the trial. These survey questions are aimed to gather broad estimates across all therapeutic areas.

### Cost for patient recruitment (monthly cost per patient in 2021 USD)

8) What is the **monthly cost required to recruit a single patient** for a clinical trial?

| Clinical trial | Cost for patient recruitment (monthly cost per patient) |
|----------------|--------------------------------------------------------|
| Average (monthly cost per patient) | |
| Minimum (monthly cost per patient) | |
| Maximum (monthly cost per patient) | |

### Cost for patient follow-up (monthly cost per patient in 2021 USD)

9) What is the **monthly cost required to follow-up on a single patient** for the following scenarios?

| Clinical trial | Cost for patient follow-up (monthly cost per patient) |
|----------------|--------------------------------------------------------|
| Average (monthly cost per patient) | |
| Minimum (monthly cost per patient) | |
| Maximum (monthly cost per patient) | |

### Cost for clinical trial site management (monthly cost per site in 2021 USD)

10) In your opinion, what is the **monthly cost required to manage a single clinical trial** for the following scenarios?

| Clinical Trial | Cost for clinical trial site management (monthly cost per site) |
|----------------|---------------------------------------------------------------|
| Average (monthly cost per site) | |
| Minimum (monthly cost per site) | |
| Maximum (monthly cost per site) | |

### Cost required for clinical trial database management (monthly cost in 2021 USD)

11) In your opinion, what is the **monthly cost required to manage a database for the following scenarios**?

| 2-arm trial | Multi-arm trial | Platform trial |
|-------------|----------------|---------------|
| Average (monthly cost) | | |
| Minimum (monthly cost) | | |
| Maximum (monthly cost) | | |

### Time required for adding new arms (in months)

12) In your opinion, how much **time is required to add a new intervention arm during a platform trial**?

| Platform Trial | Time required for adding new arms (in months) |
|----------------|---------------------------------------------|
| Average (months) | | |
| Minimum (months) | | |
| Maximum (months) | | |

### Cost required for adding new arms (in 2021 USD)

13) In your opinion, what is the **cost required to add a new intervention arm during a platform trial**?

| Platform Trial | Cost required for adding new arms (in 2021 USD) |
|----------------|-----------------------------------------------|
| Average ($) | | |
| Minimum ($) | | |
| Maximum ($) | | |
**Trial analyses:**

**Cost required for interim analyses (in 2021 USD)**

14) In your opinion, what is the **cost required to conduct a single INTERIM analysis for a single intervention in the following clinical trials** (2021 USD)?

|               | 2-arm trial | Multi-arm trial | Platform trial |
|---------------|-------------|-----------------|----------------|
| Average ($)   |             |                 |                |
| Minimum ($)   |             |                 |                |
| Maximum ($)   |             |                 |                |

**Cost required for final analysis (in 2021 USD)**

15) In your opinion, what is the **cost required to conduct the FINAL analysis for a single intervention in the following clinical trials** (2021 USD)?

|               | 2-arm trial | Multi-arm trial | Platform trial |
|---------------|-------------|-----------------|----------------|
| Average ($)   |             |                 |                |
| Minimum ($)   |             |                 |                |
| Maximum ($)   |             |                 |                |
## eTable 1. Summary of Trial Design Assumptions

| Parameter                                           | Assumption | Source                                                                 |
|-----------------------------------------------------|------------|------------------------------------------------------------------------|
| Number of sites in a platform trial                 | 120        | Sydes et al. Trials 2012, 13:168¹                                      |
| Number of sites in a multi-arm trial                | 80         | Assumed                                                                |
| Number of sites in a two-arm trial                  | 50         | Assumed                                                                |
| Annual recruitment rate per site                    | 4.167      | Annual recruitment rate calculated based on published protocol of STAMPEDE (500 patients per year / 120 = 4.167 per site) |
| Randomization ratio in a platform trial for intervention 1-5 | Unequal allocation in favor of the control (2:1) | Sydes et al. Trials 2012, 13:168¹                                     |
| Randomization ratio in a platform trial for intervention 6-10 | Equal allocation (1:1) | Sydes et al. Trials 2012, 13:168¹                                     |
| Randomization ratio in a multi-arm trial for intervention 1-5 | Unequal allocation in favor of the control (2:1) | Assumed to be the same as STAMPEDE                                    |
| Randomization ratio in a two-arm trial for intervention 1-10 | Equal allocation (1:1) | Assumed                                                                |
| Maximum sample size for an intervention             | 443        | Assumed for intervention 1-10                                          |
| Maximum sample size for the control in platform or multi-arm trial for evaluation of intervention 1-5 | 886        | Assumed for concurrent controls for intervention 1-10                  |
| Maximum sample size for the control in platform trial for evaluation of intervention 6-10 | 443        | Assumed for concurrent control for intervention 1-10                   |
| Maximum sample size for the control in two-arm trial | 443        | Assumed                                                                |
| Start time of for the first five interventions (intervention 1-5) | 0         | Relative time calculated from the start date of STAMPEDE¹ (2005-10-05): Assumed to be equal for all scenarios |
| Start time (months) for intervention 6               | 72.2       |                                                                       |
| Start time (months) for intervention 7               | 87.4       |                                                                       |
| Start time (months) for intervention 8               | 104.6      |                                                                       |
| Start time (months) for intervention 9               | 127.6      |                                                                       |
| Start time (months) for intervention 10              | 140.0      |                                                                       |
| Statistical analysis                                | Log rank test based on pairwise analysis versus concurrent control | Sydes et al. Trials 2012, 13:168; Assumed to be equal for all scenarios |
| Event rates assumptions                              | Median failure free survival (FFS) of 24 months and overall survival (OS) of 48 months | Sydes et al. Trials 2012, 13:168; Assumed to be equal for all scenarios |
| Interim analysis 1 time                              | 114 FFS events observed in concurrent control | Sydes et al. Trials 2012, 13:168¹                                     |
| Interim analysis 2 time                              | 215 FFS events observed in concurrent control | Sydes et al. Trials 2012, 13:168¹                                     |
| Interim analysis 3 time                              | 334 FFS events observed in concurrent control | Sydes et al. Trials 2012, 13:168¹                                     |
| Final analysis time                                  | 400 deaths observed in concurrent control | Sydes et al. Trials 2012, 13:168¹                                     |
| Decision rule for futility at interim analysis 1     | FFS HR of 1.0 or greater | Sydes et al. Trials 2012, 13:168¹                                     |
| Decision rule for futility at interim analysis 2     | FFS HR of 0.92 or greater | Sydes et al. Trials 2012, 13:168¹                                     |
| Decision rule for futility at interim analysis 2     | FFS HR of 0.89 or greater | Sydes et al. Trials 2012, 13:168¹                                     |
| Effect sizes for intervention 1                      | Reported FFS HR (95% CI): 0.92 (0.81, 1.04) | James et al 2016 Lancet 2016; 387: 1163–77²                             |
| Effect sizes for intervention 2                      | Reported FFS HR (95% CI): 0.61 (0.53, 0.70) | James et al 2016 Lancet 2016; 387: 1163–77²                             |
| Effect sizes for intervention 3                      | Reported FFS HR (95% CI): 0.87 (0.74, 1.03) | Mason 2017 J Clin Oncol 35:1530-1541. ³                               |
| Effect sizes for intervention 4                      | Reported FFS HR (95% CI): 0.62 (0.54, 0.70) | James et al 2016 Lancet 2016; 387: 1163–77²                             |
| Effect sizes for intervention 5                      | Reported FFS HR (95% CI): 0.84 (0.72, 0.99) | Mason 2017 J Clin Oncol 35:1530-1541. ³                               |
| Effect sizes for intervention 6                      | Reported FFS HR (95% CI): 0.29 (0.25, 0.34) | James 2017 N Engl J Med 2017;377:338-51.⁴                              |
| Effect sizes for intervention 7                      | Reported FFS HR (95% CI): 0.76 (0.68, 0.84) | Parker 2018 The Lancet. 2018 1:392(10162):2353-66.⁵                  |
| Effect sizes for intervention 8-10                   | FFS and OS HR of 0.75 (base case) | • Assumed as effect sizes not reported at the time of this study       |
|                                                     | FFS and OS HR of 1.00 (worst case) | • Target effect size used as base case from James et al. Lancet Oncol. 13: 549-58 |
|                                                     | FFS and OS HR of 0.9625 (best case) | • Best case assumes twice as large effect size as the base case on the log scale |

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eFigure 1. Schematic Diagram of the Simulation Model

The trial simulation

5000 trial "programs" are simulated

Generate Sample trial program

Simulation results (Clinical measures)

The cost and time simulation

Generate cost for the sample trial program

Simulation results (Cost and time measures)

Cost parameters (lognormal distributions with expert opinions) *
eMethods 2: Technical Details to Survey Analyses and Cost and Time Simulations

Survey analyses

Given the mean estimate and range (R) from the expert opinion: if data not normally distributed (cost parameters) then $S = R/6$ (S is the standard deviation of the distribution that we need in Step 2), according to the Chebyshev’s inequality:

$$P\left(\left|X - \mu\right| < k\sigma\right) \geq 1 - \frac{1}{k^2},$$

which results in the range covers approximately $6\sigma$, i.e., $\sigma = \frac{R}{6}$. If our data are normally distributed, then $P[-2\sigma < X - \mu < 2\sigma] = 0.95$, and therefore, the range covers approximately $4\sigma$, i.e., $\sigma = \frac{R}{4}$. Using Sigma (S) from above, R as the range from experts and (x-hat) as the mean from expert opinion, below is the equations form method of moments to use for calculating mean and standard deviation of lognormal (Cost parameters) and normal (time parameters):6

- Cost parameters: Lognormal distribution:

$$\mu = \ln(x) - \frac{1}{2}\ln\left(\frac{S^2}{\bar{x}^2} + 1\right) = \ln\left(\frac{S}{\sqrt{\frac{S^2}{\bar{x}^2} + 1}}\right)$$

$$\sigma^2 = \ln\left(\frac{S^2}{\bar{x}^2} + 1\right)$$

- Time parameters: Normal distribution- since $P[-2\sigma < X - \mu < 2\sigma] = 0.95$, and therefore, the range covers approximately $4\sigma$, i.e., $\sigma = \frac{R}{4}$.

Costing approach

We used a mixed costing approach in estimating cost of a trial. As shown, we calculated the setup cost including protocol, IRB approval, database-management, and sites in addition to recruitment cost. We next calculated the conduct cost including cost per patient follow-up for both treatment and control arms. Finally, the analysis cost for final and interim analysis were assigned.

Each sample trial simulation from OCTOPUS is used as in input to the trial cost simulator in which cost parameters associated with various resource use are utilized together with resulted sample size, number of sites and number and duration of treatments in a trial to calculate total cost of the trial. The results were then recorded for 1,000 simulations iterations (for 5 scenarios for the total of 5,000) which result in a distribution of total cost of each trial design.

The model calculates cost of each trial program by generating a cost parameter sample from the distributions of cost parameters (all lognormal distributed) and multiplying by number of patient visits (for sample-size based parameters from OCTOPUS) and number of sites/region (for fixed cost parameters). The total cost for each trial program is the summation of resource use cost for the number of patients screened, treated, and monitored, in addition to treatment costs and fixed costs for the total duration of the simulated trial program. Finally, the distribution of cost for a total of 5,000 trials programs will be constructed and reported for each trial design.
**Trial Cost Function Equation**

| Setup costs |
|-------------|
| $Total\ cost\ per\ trial = +C_{protocol} + C_{irb} + C_{database\ management} + n_{sites} \cdot C_{site}$ |
| $+ n_{controls} \cdot c_{per\ patient/recruitment}$ |

| Trial conduct costs |
|---------------------|
| $+ n_{controls} \cdot c_{per\ patient/followup} \cdot Total_{duration}$ |
| $+ \sum_{ISA} (n_{ISA} \cdot c_{recruitment\ per\ patient} +$ |
| $(+ n_{controls} \cdot c_{per\ patient/followup\ followup} + follow\ up\ time))$ |
| $(+ n_{controls} \cdot c_{per\ patient/followup\ followup} + follow\ up\ time)$ |

| Analysis costs |
|----------------|
| $+ C_{final\ analysis} + n_{interim\ analysis} \cdot C_{interim\ analysis}$ |
### eTable 2. Set-Up Cost and Time Requirements for a Platform Trial Versus Multi-Group and Two-Group Trials

| Cost (million USD) and time (years) requirements | Scenario 1: A platform trial Mean (SD) | Scenario 2: A multi-arm + two-arm trials Mean (SD) | Scenario 3: Two-arm trials Mean (SD) | Scenario 2 vs 1 Mean difference (SD) | % difference Median (IQR) | Scenario 3 vs 1 Mean difference (SD) | % difference Median (IQR) |
|------------------------------------------------|----------------------------------------|------------------------------------------|-------------------------------|--------------------------------------|--------------------------|--------------------------------------|--------------------------|
| **Set-up requirement for a single trial**      |                                        |                                          |                               |                                      |                          |                                      |                          |
| Set-up cost of a single trial                 | 2.24 (1.222)                           | 1.59 (0.82)                              | 1.09 (0.51)                   | -0.65 (0.41)                         | -26.73% (-30.80%; -25.41%) | -1.15 (0.71)                        | -48.10% (-53.47%; -46.20%) |
| Set-up time of a single trial                 | 1.305 (0.453)                          | 0.78 (0.25)                              | 0.65 (0.22)                   | -0.52 (0.52)                         | -28.18% (-55.47%; -15.59%) | -0.65 (0.5)                         | -40.80% (-64.09%; -29.78%) |
| **Cumulative set-up requirements for clinical evaluation of 10 interventions** |                                        |                                          |                               |                                      |                          |                                      |                          |
| Cumulative set-up cost                        | 2.24 (1.222)                           | 7.044 (3.383)                           | 10.902 (5.138)               | 4.803 (2.167)                        | 216.7% (202.2%; 242.4%)  | 8.662 (3.923)                       | 391.1% (365.3%; 437.9%) |
| Cumulative trial set-up time                  | 1.31 (0.45)                            | 4.05 (1.12)                             | 6.52 (2.2)                   | 2.74 (1.21)                          | 208.5% (133.1%; 330.7%)  | 5.22 (2.25)                         | 398.6% (259.3%; 601.5%) |
eFigure 2. Set-Up Cost Comparison Between Single Platform Trial, Multigroup Trial, and 2-Group Trial

Setup cost for a single platform trial vs a conventional multi-arm trial

Setup cost for a single platform trial vs a conventional 2-arm trial
eFigure 3. Total Cumulative Set-Up Costs Comparison Between Design Scenarios: A Single Platform Trial vs a Multigroup Plus 2-Group Trials and 2-Group Trials

Setup cost for a single platform trial vs conventional multi- and 2-arm trials

Cumulative total setup costs for conventional multi- and 2-arm trials for 10 interventions

Setup cost for a single platform trial vs conventional 2-arm trials

Cumulative total setup costs for conventional 2-arm trials for 10 interventions
### eTable 3. Total Cumulative Trial Duration and Costs Between Different Clinical Design Scenarios

| Cost (million USD) and time (years) requirements | Scenario 1: A platform trial Mean (SD) | Scenario 2: A multi-arm + two-arm trials Mean (SD) | Scenario 3: Two-arm trials Mean (SD) | Scenario 2 vs 1 Mean difference (SD) | % difference Median (IQR) | Scenario 3 vs 1 Mean difference (SD) | % difference Median (IQR) |
|------------------------------------------------|----------------------------------------|-------------------------------------------------|-------------------------------------|--------------------------------------|--------------------------|-------------------------------------|--------------------------|
|                                                 |                                         |                                                 |                                     | **Base case**                        |                          | **Base case**                        |                          |
| Total cumulative trial duration for all 10 interventions (1-10) | 20.75 (1.16)                          | 55.96 (3.38)                                    | 85.85 (8.56)                       | 35.21 (3.52)                        | 171.1% (158.3%; 184.3%) | 65.09 (8.58)                        | 311.9% (282%; 349.1%)   |
| Total cumulative trial duration for first five interventions (1-5) | 5.96 (0.19)                           | 8.1 (0.58)                                      | 37.99 (7.48)                       | 2.14 (0.61)                         | 36.1% (30.8%; 41.5%)    | 32.03 (7.48)                       | 526.3% (429.4%; 657.9%) |
| Total cumulative trial duration for last five interventions (6-10) | 14.74 (1.16)                          | 47.86 (3.35)                                    | 47.86 (3.35)                       | 33.12 (3.49)                        | 226.7% (206.8%; 246.7%) | 33.12 (3.49)                       | 226.7% (206.8%; 246.7%) |
| Total trial cost for all interventions (1-10) | 104.951 (32.512)                      | 122.105 (36.744)                                | 163.403 (51.042)                   | 17.154 (10.569)                     | 17.4% (12.1%; 22.5%)   | 58.452 (24.942)                    | 57.7% (43.1%; 69.9%)    |
| Total trial cost for first five treatments (1-5) | 31.356 (9.022)                        | 40.403 (15.277)                                 | 81.701 (25.521)                    | 9.047 (10.159)                      | 28% (5.5%; 50.1%)      | 50.345 (17.957)                    | 158.4% (136.9%; 184.1%) |
| Total trial cost for last five treatments (6-10) | 73.594 (23.893)                       | 81.701 (25.521)                                 | 81.701 (25.521)                    | 8.107 (10.6)                        | 12.6% (2.1%; 22.6%)    | 8.107 (10.6)                       | 12.6% (2.1%; 22.6%)    |
| Trial management cost for evaluation of first five interventions (1-5) | 3.876 (2.035)                         | 3.155 (1.67)                                    | 7.756 (5.324)                      | -0.722 (0.431)                      | -18.3% (-21.1%; -15.9%)| 3.88 (4.059)                       | 92.7% (11.7%; 198.2%)  |
| Trial management cost for evaluation of last five interventions (6-10) | 8.638 (4.613)                         | 7.756 (5.324)                                   | 7.756 (5.324)                      | -0.882 (3.696)                      | -14.1% (-45.8%; 30%)  | -0.882 (3.696)                      | -14.1% (-45.8%; 30%)  |
|                                                 |                                         |                                                 |                                     | **Pessimistic case**                |                          | **Pessimistic case**                |                          |
| Total cumulative trial time for all 10 interventions (1-10) | 15.95 (1.53)                          | 39.17 (5.96)                                    | 58.47 (7.38)                       | 23.21 (6.17)                        | 144.2% (116.3%; 173.4%)| 42.52 (7.45)                       | 266% (232.6%; 303.8%)  |
| Total cumulative trial time for first five interventions (1-5) | 5.9 (0.53)                            | 7.29 (1.43)                                     | 26.6 (4.18)                        | 1.4 (1.51)                          | 26.9% (21.1%; 32.6%)  | 20.7 (4.21)                        | 334.5% (298.9%; 389.9%)|
| Total cumulative trial time for first five interventions (6-10) | 9.94 (1.53)                           | 31.87 (5.78)                                    | 31.87 (5.78)                       | 21.93 (5.99)                        | 220.4% (176.5%; 271.3%)| 21.93 (5.99)                       | 220.4% (176.5%; 271.3%)|
| Total trial cost for all interventions (1-10) | 70.945 (21.549)                       | 80.254 (26.483)                                 | 101.967 (32.599)                   | 9.309 (16.519)                      | 13% (-1.8%; 27.9%)    | 31.022 (20.27)                     | 43.8% (25.7%; 63.9%)   |
| Total trial cost for first five treatments + concurrent control | 27.123 (7.977)                        | 29.27 (12.571)                                  | 50.984 (16.299)                    | 2.147 (9.989)                       | 5.9% (-14.9%; 27.8%)  | 23.861 (11.333)                    | 82.8% (62.4%; 107.3%)  |
| Total trial cost for last five treatments + concurrent control | 43.822 (14.605)                       | 50.984 (16.299)                                 | 50.984 (16.299)                    | 7.162 (11.035)                      | 17.1% (1.1%; 36%)  | 7.162 (11.035)                     | 17.1% (1.1%; 36%)    |
| Trial management cost for evaluation of first five interventions (1-5) | 3.876 (2.035)                         | 2.811 (1.643)                                   | 4.704 (2.945)                      | -1.065 (0.824)                      | -24.3% (-27.3%; -21.5%)| 0.827 (1.723)                      | 2% (-2.8%; 40.8%)     |
| Trial management cost for evaluation of last five interventions (6-10) | 5.54 (3.037)                          | 4.704 (2.945)                                   | 4.704 (2.945)                      | -0.836 (1.91)                       | -21% (-33.5%; -2.5%) | -0.836 (1.91)                      | -21% (-33.5%; -2.5%)  |
### Scenario 1: A platform trial

| Scenario 1: A platform trial       | Scenario 2: A multi-arm + two-arm trials | Scenario 3: Two-arm trials | Scenario 2 vs 1 | Scenario 3 vs 1 |
|-----------------------------------|------------------------------------------|-----------------------------|-----------------|-----------------|
| Mean (SD)                         | Mean (SD)                                | Mean (SD)                   | Mean difference (SD) | Mean difference (SD) |
| Total cumulative trial time for all 10 interventions (1-10) | Total cumulative trial time for first five interventions (1-5) | Total cumulative trial time for first five interventions (6-10) | Total trial cost for all interventions (1-10) | Total trial cost for first five treatments + concurrent control |
| 20.83 (1.03)                      | 6.03 (0.21)                              | 14.82 (1.03)                | 111.02 (34.322)  | 34.526 (9.938)   |
| 57.17 (1.95)                      | 8.37 (0.37)                              | 48.79 (1.9)                 | 131.328 (39.654) | 36.09 (12.426)   |
| 96.25 (5.42)                      | 47.46 (4.74)                             | 48.79 (1.9)                 | 190.476 (58.02)  | 95.238 (29.01)   |
| 36.33 (2.18)                      | 2.34 (0.42)                              | 33.98 (2.13)                | 20.308 (7.654)   | 1.564 (6.476)    |
| **Mean difference (SD)**          | **Mean difference (SD)**                 | **Mean difference (SD)**    | **Mean difference (SD)** | **Mean difference (SD)** |
| 175.4% (164.4%; 186%)             | 38.7% (33.9%; 44%)                      | 230.8% (213.8%; 248.7%)    | 79.456 (25.584)  | 60.712 (19.73)   |
| **% difference**                  | **% difference**                         | **% difference**            | **% difference**  | **% difference**  |
| 365.6% (345.4%; 386.8%)           | 703.3% (673%; 733.8%)                   | 230.8% (213.8%; 248.7%)    | 75.42 (5.48)     | 41.42 (4.74)     |

The estimated total duration included time required to set-up and conduct times. The total trial cost included all costs required to set up and conduct the trial.

For interventions with reported treatment effects (hazard ratio [HR] and 95% confidence intervals) on FFS and OS, we used the point estimate as the ‘base case’, the lower confidence interval as the ‘best case’, and the upper confidence interval as the ‘pessimistic case’ for our simulations. For the last three intervention arms without reported results, we assumed the base case FFS and OS to have HR of 0.75, which was the target treatment effects by the STAMPEDE investigators. The best case scenario for these intervention arms assumed a treatment effect of 0.5625, twice as large treatment effects as the target effects, for both FFS and OS, and the pessimistic case scenario assumed that these interventions would have no treatment effects on either outcomes (HR = 1.00).
eFigure 4. Total Cumulative Trial Duration Comparisons Between a Platform Trial Versus Conventional Trials

a) Base case

For interventions with reported treatment effects (hazard ratio [HR] and 95% confidence intervals) on FFS and OS, we used the point estimate as the ‘base case’, the lower confidence interval as the ‘best case’, and the upper confidence interval as the ‘pessimistic case’ for our simulations. For the last three intervention arms without reported results, we assumed the base case FFS and OS to have HR of 0.75, which was the target treatment effects by the STAMPEDE...
investigators. The best case scenario for these intervention arms assumed a treatment effect of 0.5625, twice as large treatment effects as the target effects, for both FFS and OS, and the pessimistic case scenario assumed that these interventions would have no treatment effects on either outcomes (HR = 1.00).
# eTable 4. Estimated Sample Sizes Between Different Clinical Design Scenarios

| Estimated sample size | Scenario 1: A platform trial Mean (SD) | Scenario 2: A multi-arm + two-arm trials Mean (SD) | Scenario 3: Two-arm trials Mean (SD) | Scenario 2 vs 1 Mean difference (SD) | % difference Median (IQR) | Scenario 3 vs 1 Mean difference (SD) | % difference Median (IQR) |
|-----------------------|----------------------------------------|------------------------------------------|-------------------------------------|-------------------------------------|--------------------------|-------------------------------------|--------------------------|
| **Base case**         |                                        |                                          |                                     |                                     |                          |                                     |                          |
| No. of total patients randomized to treatments 1-10 | 4018.26 (193.659) | 3783.621 (149.874) | 4258.903 (242.555) | -234.639 (240.732) | -6% (-9.4%; -2%) | 240.643 (319.232) | 6.9% (1.2%; 11.4%) |
| No. of patients randomized to treatments 1-5 | 1811.181 (190.705) | 1582.874 (137.346) | 2208.64 (70.526) | -228.307 (230.855) | -13% (-19.8%; -4.7%) | 397.459 (204.826) | 20.8% (14%; 30.6%) |
| No. of patients randomized to treatments 6-10 | 2207.079 (27.005) | 2208.64 (70.526) | 1.561 (76.184) | 0% (0%; 0%) | 1.561 (76.184) | 0% (0%; 0%) |
| No. of total control patients for evaluation of all treatments (1-10) | 2574.461 (81.019) | 2949.383 (86.377) | 4252.62 (237.345) | 374.922 (118.257) | 14.8% (12%; 17.7%) | 1678.159 (248.058) | 67.8% (58.3%; 72.7%) |
| No. of concurrent control patients for treatment 1-5 | 881.288 (47.175) | 753.775 (63.997) | 2203.375 (71.774) | -127.513 (80.255) | -14.6% (-19.2%; -6.6%) | 1322.087 (86.811) | 150.3% (141.2%; 160.6%) |
| No. of concurrent control patients for treatment 6-10 | 1693.173 (60.097) | 2203.375 (71.774) | 510.202 (94.898) | 30.5% (27.5%; 33.6%) | 510.202 (94.898) | 30.5% (27.5%; 33.6%) |
| **Pessimistic case**  |                                        |                                          |                                     |                                     |                          |                                     |                          |
| No. of total patients randomized to treatments 1-10 | 3519.609 (227.11) | 3205.556 (312.262) | 3619.2 (353.839) | -314.053 (399.004) | -9% (-16.1%; -0.8%) | 99.591 (428.472) | 2.9% (-5.6%; 10.9%) |
| No. of patients randomized to treatments 1-5 | 1444.448 (209.455) | 1303.194 (178.23) | 1751.83 (422.971) | -141.254 (282.929) | -5.4% (-20.5%; 2.5%) | 307.382 (481.275) | 23.9% (-9%; 50.3%) |
| No. of patients randomized to treatments 6-10 | 2075.161 (82.926) | 1751.83 (422.971) | 1751.83 (422.971) | -323.331 (433.558) | -9% (-35.7%; 4.9%) | -323.331 (433.558) | -9% (-35.7%; 4.9%) |
| No. of total control patients randomized to control | 2545.851 (104.65) | 2694.985 (307.17) | 3622.611 (347.691) | 149.134 (324.763) | 5.9% (-3.3%; 16.7%) | 1076.35 (359.154) | 42.7% (30.9%; 51.5%) |
| No. of concurrent control patients for treatment 1-5 | 888.551 (87.237) | 791.654 (169.9) | 1755.775 (415.109) | -96.897 (188.617) | -7.4% (-13.2%; -2.8%) | 867.224 (426.602) | 109.4% (48.4%; 142.7%) |
| No. of concurrent control patients for treatment 6-10 | 1657.3 (60.77) | 1755.775 (415.109) | 98.475 (417.701) | 13.5% (-19.1%; 31.5%) | 98.475 (417.701) | 13.5% (-19.1%; 31.5%) |
| **Best case**         |                                        |                                          |                                     |                                     |                          |                                     |                          |
| No. of total patients randomized to treatments 1-10 | 4216.884 (122.664) | 3925.333 (95.94) | 4406.308 (102.787) | -291.551 (153.757) | -7.2% (-9.1%; -4.8%) | 189.424 (157.72) | 4.4% (2.8%; 6.6%) |
| No. of patients randomized to treatments 1-5 | 2002.8 (122.089) | 1711.381 (94.821) | 2215 (0) | -291.419 (152.653) | -15% (-18.9%; -10.2%) | 212.2 (122.089) | 6.8% (6.3%; 14.4%) |
| No. of patients randomized to treatments 6-10 | 2214.084 (9.352) | 2215 (0) | 2215 (0) | 0.916 (9.352) | 0% (0%; 0%) | 0.916 (9.352) | 0% (0%; 0%) |
| No. of total patients randomized to control | 2501.431 (84.65) | 2921.378 (33.944) | 4396.531 (101.475) | 419.947 (91.861) | 16.6% (14.1%; 19.5%) | 1895.1 (133.15) | 76.1% (72.4%; 80.1%) |
| No. of concurrent control patients for treatment 1-5 | 832.468 (39.93) | 712.52 (30.892) | 2210.03 (7.076) | -119.945 (51.398) | -14.3% (-17.8%; -10.8%) | 1377.56 (40.8) | 167.6% (158.5%; 174.5%) |
| No. of concurrent control patients for treatment 6-10 | 1668.963 (71.202) | 2210.03 (7.076) | 541.067 (71.181) | 31.9% (28.9%; 35.8%) | 541.067 (71.181) | 31.9% (28.9%; 35.8%) |
For interventions with reported treatment effects (hazard ratio [HR] and 95% confidence intervals) on FFS and OS, we used the point estimate as the ‘base case’, the lower confidence interval as the ‘best case’, and the upper confidence interval as the ‘pessimistic case’ for our simulations. For the three intervention arms without reported results, we assumed the base case FFS and OS to have HR of 0.75, which was the target treatment effects by the STAMPEDE investigators. The best case scenario for these intervention arms assumed a treatment effect of 0.5625, twice as large treatment effects as the target effects, for both FFS and OS, and the pessimistic case scenario assumed that these interventions would have no treatment effects on either outcomes (HR = 1.00).
| Simulated follow-up time (months): | Scenario 1: A platform trial Mean (SD) | Scenario 2: A multi-arm + two-arm trials Mean (SD) | Scenario 3: Two-arm trials Mean (SD) | Scenario 2 vs 1 | Scenario 3 vs 1 |
|-----------------------------------|--------------------------------------|-----------------------------------------------|------------------------------------|----------------|----------------|
| Mean difference (SD)              | % difference (IQR)                    | Mean difference (SD)                          | % difference (IQR)                  |                 |                |
| **Base case**                     |                                      |                                               |                                   |                 |                |
| Total follow-up for patients      | 43958.745 (6650.624)                 | 116314.288 (11223.959)                       | 201.969 (8996.695)                 | 1.4% (13.9%; 17%) | 72355.543 (13119.187) |
| randomized to treatments 1-5      | (months)                             | (months)                                      | (months)                           |                 | (168.3% (141.8%; 196%) |
| Total follow-up for patients      | 82192.52 (5195.373)                  | 116314.288 (11223.959)                       | 34121.768 (12233.675)              | 42.1% (35.2%; 48.8%) | 34121.768 (12233.675) |
| randomized to treatments 6-10     | (months)                             | (months)                                      | (months)                           |                 | (42.1% (35.2%; 48.8%) | |
| Total follow-up for concurrent    | 21820.179 (1908.674)                 | 102920.136 (10226.48)                        | -986.999 (2643.762)                | -3.6% (-10.6%; 3.3%) | 81099.957 (10366.77) |
| control for treatments 1-5        | (months)                             | (months)                                      | (months)                           |                 | (377.9% (343.5%; 413%) | |
| Total follow-up for concurrent    | 101095.08 (6621.422)                 | 102920.136 (10226.48)                        | 1825.056 (12130.723)               | 2% (-3.5%; 7.9%) | 1825.056 (12130.723) |
| control for treatments 6-10       | (months)                             | (months)                                      | (months)                           |                 | (2% (-3.5%; 7.9%) | |
| **Pessimistic case**              |                                      |                                               |                                   |                 |                |
| Total follow-up for patients      | 31072.933 (6450.291)                 | 39668.452 (25703.098)                        | -2185.094 (9449.75)                | -8.7% (-22.9%; 13%) | 8595.52 (26725.613) |
| randomized to treatments 1-5      | (months)                             | (months)                                      | (months)                           |                 | (5.2% (-44.8%; 90.8%) | |
| Total follow-up for patients      | 45009.443 (8147.032)                 | 39668.452 (25703.098)                        | -5340.991 (26945.978)              | -28% (-60.3%; 33.2%) | -5340.991 (26945.978) |
| randomized to treatments 6-10     | (months)                             | (months)                                      | (months)                           |                 | (-28% (-60.3%; 33.2%) | |
| Total follow-up for concurrent    | 23522.288 (3685.128)                 | 39091.305 (24813.567)                        | -4340.66 (5690.323)                | -16.4% (-22.6%; -9.6%) | 15569.017 (25151.502) |
| control for treatments 1-5        | (months)                             | (months)                                      | (months)                           |                 | (38% (-26.1%; 150.1%) | |
| Total follow-up for concurrent    | 56866.417 (10877.751)                | 39091.305 (24813.567)                        | -17775.112 (28901.962)             | -43.9% (-68.5%; 2.4%) | -17775.112 (28901.962) |
| control for treatments 6-10       | (months)                             | (months)                                      | (months)                           |                 | (-43.9% (-68.5%; 2.4%) | |
| **Best case**                     |                                      |                                               |                                   |                 |                |
| Total follow-up for patients      | 53979.925 (5579.283)                 | 129366.694 (6516.321)                        | 1295.446 (7960.05)                 | 2% (-6.4%; 12.1%) | 75386.769 (8501.664) |
| randomized to treatments 1-5      | (months)                             | (months)                                      | (months)                           |                 | (138.1% (121.7%; 156.7%) | |
| Total follow-up for patients      | 88328.665 (3909.603)                 | 129366.694 (6516.321)                        | 41038.029 (7424.752)               | 46.5% (40.5%; 52.9%) | 41038.029 (7424.752) |
| randomized to treatments 6-10     | (months)                             | (months)                                      | (months)                           |                 | (46.5% (40.5%; 52.9%) | |
| Total follow-up for concurrent    | 20941.786 (1377.681)                 | 103868.517 (5956.312)                        | 45.462 (1769.345)                  | 0.4% (-4.9%; 6.3%) | 82926.731 (6123.275) |
| control for treatments 1-5        | (months)                             | (months)                                      | (months)                           |                 | (397.4% (369.5%; 425.5%) | |
| Total follow-up for concurrent    | 103905.838 (4162.234)                | 103868.517 (5956.312)                        | -37.321 (7270.004)                 | -0.4% (-4.5%; 4.8%) | -37.321 (7270.004) |
| control for treatments 6-10       | (months)                             | (months)                                      | (months)                           |                 | (-0.4% (-4.5%; 4.8%) | |

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