Supplementary Online Content

Moore TJ, Zhang H, Anderson G, Alexander GC. Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016. *JAMA Intern Med.* Published online September 24, 2018. doi:10.1001/jamainternmed.2018.3931

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

This supplement to “Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016” provides additional detail about variable definitions and how the cost estimates were created using the IQVIA CostPro Mid-Level Tool.

Industry Cost Benchmark Data

The IQVIA CostPro Mid-Level Tool estimates were based in part on industry benchmark cost data from more than 2 000 clinical trial contracts. This supporting data spanned all 8 therapeutic areas specifically reported in this study, with a maximum of 18% of the contracts in the oncology therapeutic area, and a minimum of 3% of the site budgets for the dermatology area. The underlying site data included agreements from all 8 geographic regions. North America had the largest share (59%) and Oceania the smallest (2%). (IQVIA Clinical Trial Optimization Solutions, email communication, May 2018)

Detailed Assumptions

If a trial combined phases (such as phase 2/3) we coded it as the higher phase. If a trial had two or more parts with a crossover or similar design, we estimated total patients enrolled using the initial study group assignments. The duration of the trial was based on the time period in weeks over which patients were systematically observed to assess benefit. We used the duration in weeks that the FDA relied on for approval even if the trial was scheduled to continue. The number of patient visits included screening, run-in periods, randomization, and treatment follow-up visits. For cost purposes, the number of months during which sites enrolled and treated patients was calculated as

the difference between the study start date and the primary completion date reported in ClinicalTrials.gov. Open label follow-ups and other kinds of extensions were not included in either trial duration or number of visits. Primary end points were the first listed primary end point in ClinicalTrials.gov, except that if both safety and efficacy end points were listed, the first listed efficacy end point was selected. Pivotal trial cost estimates were reported in millions of current US dollars to one decimal place. CostPro default values were used for a few trials where the number of patients screened was not disclosed; one screening visit was assumed when the number of screening visits was not specified.

Allocation by Region

Evaluation tests of the IQVIA CostPro Mid-Level estimating tool showed a substantial difference in site costs by regions. We used a standard geographical listing to code country information to into the following 8 regions: North America, Latin America, Western Europe, Central Europe, Middle East, Africa, Asia and Oceania. The following rules were applied to missing or inconsistent country, site, and region data from the different sources: 1) In some instances, source documents used different definitions of regions; in those cases, we reallocated them to 8 standard regions using the number of sites or patients per country. 2) In other instances, the source documents disclosed the number of patients per country but only overall global total of study sites; in these cases, we allocated sites based on the percentage of patients treated in each country. 3) If the source documents disclosed region or country-specific data on sites but not patient totals by country we allocated patients by region based on the number of sites in each region. 4) In a few pivotal trials, the only allocation information available

was that they were international in character; in these instances, we allocated by region, patient and site using the aggregate percentages for all other pivotal trials for which complete data were available. We limited the number of languages for translation to one language per country, based on that country's predominant language.

The following trial costs were assumed to be centralized in the CRO: biostatistics, medical writing, data management, project management, and clinical trial document preparation. If the trial included sites in North America, the centralized costs were allocated to that region; if there were no North American sites, centralized costs were allocated to the region with the largest proportion of patients.

Default Trial Conduct Efficiency Assumptions

For purposes of estimating likely costs we assumed that all the pivotal trials were conducting using widely available technologies intended to lower costs of clinical trials. Specifically, we assumed that all trials used Interactive Voice Recognition Systems (IVRS) for randomization, listings, reports and data transfers. We also assumed that electronic data capture (EDC) systems had replaced paper records. In addition, we assumed the hypothetical CRO was responsible for supplying, shipping, and packaging drugs. However, the cost of manufacturing the drugs was not included and could not be determined.

Variable Trial Conduct Efficiency Assumptions

The 6 variables to capture differences in efficiency of the conduct of the trials contained the following assumptions, listed as less efficient/higher cost or more efficient/lower cost:

1) Length of start-up: 6 months vs 3 months

2) Length of close-out: 6 months vs 3 months

3) IRBs: 1 per site vs 1 central IRB per region

4) Protocol amendments: 3 data changes vs 0 data changes

5) Weeks between monitoring visits: 4 weeks versus 8 weeks

eTable. Specific CostPro Inputs

eTable 1 shows the clinical trial inputs used to calculate low-median-high estimates with the IQVIA CostPro Mid-Level Tool

eTable 1. CostPro Inputs
Trial characteristics
ICD 9 Code
Phase
Length of project
Number of evaluable subjects*
Total number of subjects screened
Number of sites
Number of visits per subject
Number of central IRB's
Number of local IRB's
Length of start up
Length of study conduct (FPFV-LPLV)**
Length of study close out phase
Languages for translation
Weeks between each monitoring visit
Is drug refrigerated
Data blinded
Number of data changes
Patient allocation (countries, patients, sites)
Africa
Asia
Central Europe
Latin America
Middle East
North America
Oceania
Western Europe
Category allocation (by region %)
Regionally allocated
Pass-through costs
Study conduct
Site management
Regulatory
Centrally allocated tasks***
Project management
Clinical trial document preparation
Biostatistics
Medical writing
Data management
Italic identifes higher or lower efficiency cost variables
* Assumed as number randomized
**FPFV = first patient first visit; LPLV = last patient last visit
***To North America if any sites in region