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Cardiovascular outcome trials: strategic insights for country and site distribution.

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Driving study completion in a cardiovascular outcome trial (CVOT) requires extensive planning from the onset to prevent costly errors from remediation, avoid prolonged enrollment periods and minimize delayed or reduced event occurrence. Drug development sponsors need to begin with the end in mind to capture the right endpoints, including targeted patient populations for labeling purposes and securing the trial to include patients who would most benefit from the study drug to ensure a potential market.

To help drug development sponsors run an efficient CVOT, this white paper shares key operational considerations and describes the use of proprietary tools and processes combined with information in the public domain to support both country and site selection.

Examining country selection factors in a CVOT

Selection of countries in a large CVOT trial is key to success due to the high number patients who need to be enrolled quickly. These studies involve a large number of countries that represent all regions globally to support the study drug's registration. More recently studies have included China and Japan, the latter of which is associated with higher costs. It is important to note that the approval of a drug in some countries will also require a defined percent of patients contributed by that country. Therefore, pre-planning will require interaction with the regulatory agencies (i.e., FDA, EMA, NMPA, PMDA) ahead of the trial start, so drug development sponsors can understand the requirements for the region and/or country to participate and eventually support marketing approval.

Evaluating the cost factors in a CVOT

Associated cost represents another key factor for selecting countries in a large CVOT. A country and the sites selected within the country influence investigator grant rates based on the country's cost of living and locality, laboratory shipping requirements, drug storage and distribution requirements, as well as cost of resources in a country supporting the study, i.e., clinical research associates (CRAs).

Study design and required procedures impact study costs; however, if there is scientific interest in the drug, publication possibilities or the influence of well-respected key opinion leaders (KOLs), grants may be negotiated. Based on our experience at Fortrea, placement of large CVOTs in Eastern European and Latin American countries reduces cost as sites in these countries can be high recruiters – and have much lower costs than the US or Western Europe.

While some large CVOTs choose to concentrate the location of the study with a large number of sites in just a few countries to maximize resource efficiency and decrease some costs, it may also result in the inclusion of some lower-performing sites. Choosing the best-performing sites across a wider geography often improves study timelines and site-level efficiency as the number of non-performing sites is reduced.

Understanding country-specific factors that influence trial design

Standard of care by country should be considered when selecting potential countries. In-country leadership and site outreach provides insights to standard of care and potential risks of study design to implementation in that country. This approach can lead to a more refined country selection, if needed, or the opportunity to plan ahead and mitigate risk. Figure 1 represents standard-of-care differences among a selection of countries that may influence the decision to include a country, as site enrollment patterns may vary. In the TOPCAT trial (*Circulation.* 2015 Jan 6;131(1):34-42.), for example, the analysis was impacted by high enrollment of patients in Russia (RUS) and Georgia (GEO), where standard of care differed.

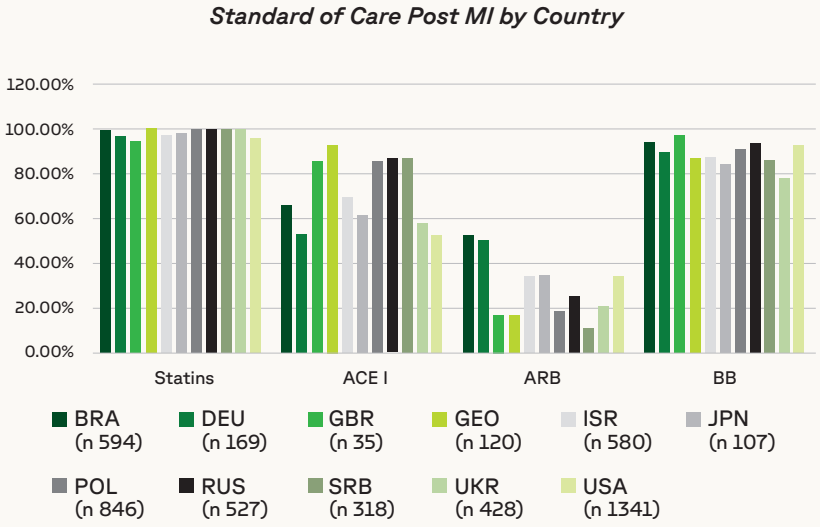

Figure 1: Standard of Care Differences Among a Selection of Countries

In another example (Figure 2), the length of stay in the hospital is shown to vary among countries, a factor which may impact study results. For example, if patients are reporting fewer events in countries, it may be associated with longer hospital stays compared to other countries; sponsors should understand this risk ahead of study implementation and create an appropriate plan to control for this factor. It would be prudent to monitor enrollment trends and event rates while the study is ongoing and mitigate the risk by capping countries/regions.

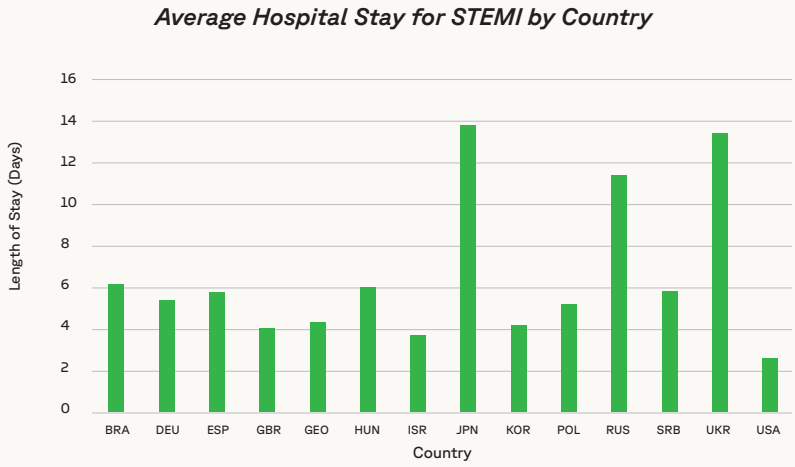

Figure 2: Length of Hospital Stay for ST-Elevation Myocardial Infarction (STEMI) by Country

Identifying the best sites

Once a country is selected, the process of identifying the sites becomes a critical component in the implementation of the trial. Lack of enrollment is a leading reason for trial delays. Enrollment performance across investigators, sites and countries can be reviewed by targeting previous "like"-trials.

To help sponsors refine country and site lists, Fortrea uses the Investigator Performance Strategy Tool (IPST) that accesses Central Laboratory Data from over 40% of all clinical trials across the globe. These data enable identification of higher-performing countries and sites, as indicated in Figure 3. By selecting top-performing sites – and eliminating nonperformers – a more efficient/effective study can be designed.

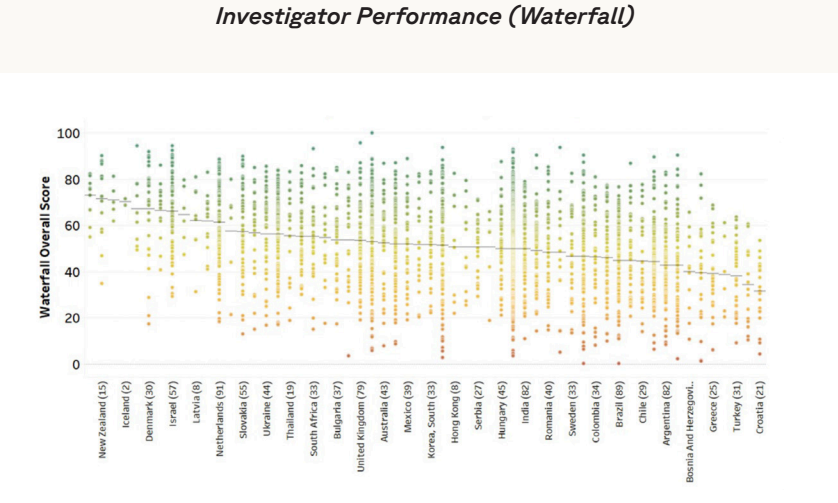

Figure 3: Investigator Performance Ranking by Country

Realizing the benefits of upfront planning

Planning a large CVOT requires careful consideration of the study design, country and site selection, key factors that impact delivery and cost of the trial. Investing ample time in the planning stages will help minimize country-specific differences that impact the number of patients enrolled. Fortrea has the expertise, the tools and processes to support planning and active management of a CVOT. We work collaboratively with sponsors and their key stakeholders to start with the end in mind and maximize study efficiency.

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