We selected NDAs with an imbalance in the racial subgroups in the analyzed populations that also submitted screen failure data in DM and IE domains. We assessed the criteria for screen failure by evaluating nonconformance to inclusion criteria or conformance with an exclusion criterion by subject. We then summarized the reason for screen failure by racial category.

RESULTS:

Of 28 NDAs assessed through JumpStart in 2015, 22 (~78%) submitted screen failure records in the DM domain and 16 (57%) also contained a BIMO dataset. A total of 15 applications (~53% of NDAs) included the reason for screen failures, citing the relevant inclusion and exclusion criteria provided in the Trial Design (TD) dataset in at least 80% of subjects.

One NDA provided screen failure data from the Phase 2/3 trial pool for about 20,000 screened patients of which about 10,000 were enrolled. Nonconformance to inclusion criteria for screen failures represented 50% (n=5360) and conformance to exclusion criteria represented 50% (n=5296).

Another 25% (n=2576) did not have any data on the exclusion and inclusion criteria. The integrated dataset consisted of heterogeneous trials with a diverse array of inclusion and exclusion criteria, requiring reclassification for this presentation. For example, the following are some of the terms that were reclassified to the category of Cardiovascular Disease:

- Hypertension
- Arrhythmia
- Significant Cardiovascular History Within The Past 6 Months Prior To Enrolment
- Myocardial Infarction
- Recent Cardiovascular Events in a Patient

The review identified 12,000 unique patients across 2576 NDAs. The most frequently used criteria included:

- Hypertension
- Myocardial Infarction
- Arrhythmia
- Recent Cardiovascular Events in a Patient

When we compared the gold standard criteria and newly identified criteria, 3,000 patients were reclassified.

Inclusion and exclusion criteria for the same concept could be further specified to reduce screening ambiguity. For example, the set of criteria below does not describe how subjects who fit between the test thresholds included in the inclusion and the exclusion criteria should be handled:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Microalbumin / Creatinine Ratio &lt; 300 mg/g (Note also the non-standard capitalization of units in the original submission)</td>
<td>Urine Albumin/Creatinine Ratio (UACR) &gt; 1,800 mg/g (203.4 mg/mmol/Cr)</td>
<td></td>
</tr>
</tbody>
</table>

A fair amount of patients who fulfilled exclusion criteria nonetheless received treatment as documented by using a Patient Profile Viewer (See Figure)

DISCUSSION:

Screen failure data are helpful in understanding the generalizability of the results from subjects who participate in clinical trials. Underlying conditions may cause subject exclusion, such as hepatic abnormalities. Interestingly, renal disease was notable in the Asian group as an exclusion criteria. Creatine kinase (CK) elevations in Black subjects caused more exclusions, but renal dysfunction was not disproportionate in the Black group relative to other racial categories. It is important when possible to use the race-specific normal range for test analytes when they exist, such as for CK.

Screen failure data can help in managing post-marketing risk; an assessment of adverse events that occur in subjects who receive therapy and fail screening is necessary, as similar subjects may receive the drug when marketed. Screening criteria can probably be modified to encourage inclusion of subjects generally excluded from clinical trials. In addition, pragmatic, real world studies or trials in special population may supplement the missing/limited subgroup information resulting from screen failures.

REFERENCES:

3. CI CW 325 60.

DISCLAIMER: The views expressed in this presentation are those of the authors and do not represent the policy of FDA.