Using baseline CrCL as an example covariate, this study will demonstrate that the relationship between the CPI and drug clearance (CCL) can be used as an instructive example for investigating how the statistical properties of the covariate submodel are impacted by population PK models. Because there are well-defined categories of renal impairment, a clinical significance ratio (CSR) can be constructed as a guide to the clinical importance of the covariate effect. For our purposes, CSR was defined as the ratio of the population estimated typical value of CrCL in moderate renal dysfunction compared to normal renal function:

\[
\text{CSR} = \frac{\text{CrCL}_{\text{mod}}}{\text{CrCL}_{\text{nor}}} = \frac{1.15 \times \text{CrCL}_{\text{nor}}}{\text{CrCL}_{\text{nor}}} = 1.15
\]

The probability of demonstrating that:

\[
\alpha \leq 0.05 \quad \text{is dependent on the following formula:}
\]

\[
\text{CSR} - 1.96 \sqrt{\frac{\text{V}^2}{n}} = 0
\]

is the corrected sum of squares for the covariate (a measure of the diversity of the covariate in the dataset). Hence, the basic statistical properties of the covariate submodel alone indicate that the probability of detecting a covariate relationship is dependent on the true value of the covariate and the statistical significance (p-value).

The relationship between creatinine clearance (CCL) and drug clearance (CCL) can be used as an instructive example for investigating how the statistical properties of the covariate submodel are impacted by population PK models. Because there are well-defined categories of renal impairment, a clinical significance ratio (CSR) can be constructed as a guide to the clinical importance of the covariate effect. For our purposes, CSR was defined as the ratio of the population estimated typical value of CrCL in moderate renal dysfunction compared to normal renal function:

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<table>
<thead>
<tr>
<th>Scenario 1 (CSS = 27600), True CSR = 0.9</th>
<th>Scenario 2 (CSS = 38900), True CSR = 0.9</th>
<th>Scenario 3 (CSS = 45300), True CSR = 0.9</th>
<th>Scenario 4 (CSS = 83100), True CSR = 0.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVCL at CrCL = 45 ml/min</td>
<td>TVCL at CrCL = 45 ml/min</td>
<td>TVCL at CrCL = 45 ml/min</td>
<td>TVCL at CrCL = 45 ml/min</td>
</tr>
</tbody>
</table>

**RESULTS**

Example results for sparse sampling (n = 5) and N = 100 are provided below. The percent reduction in IV increased with increasing CSS and was greater for true CSR values of 0.9 and 0.8 than for 0.7 and 0.6. Clinical significance was under estimated, but seemed to plateau for values of true CSR > 0.9. As shown in Figure 4, p-values for the null case averaged about 0.5, as expected, while p-values for non-null cases usually indicated statistical significance (mean < 0.01 and maximum < 0.1). The results for true CSR < 0.8, which were all much less than 0.5, are not shown.

The relative standard error (%SEM) values generally decreased as true CSR decreased from 0.9 to 0.8 to 0.7 and 0.6, and as expected, also decreased with increasing CSS. Clinical significance was achieved with %SEM values for the linear parameter in the 5% to 25% range, while %SEM values much higher in absolute value were seen mainly when clinical significance was lacking. Because the power parameter coefficient estimates were very small and could be positive or negative, values of %SEM for the null case (not shown) ranged much more widely with 25th and 75th percentiles of 136% and 123% for CSS = 27,600.

For N = 50 were essentially the same as those for N = 100, and results for full profile (n = 12) and sparse sampling (n = 5) data were similar. The results for the linear covariate model were essentially the same for the power model as well, and as the slope increased, the linear models had more non-convergent runs than the power model with N = 100 and sparse sampling (n = 5); the number of non-convergent runs was 500 for all cases when true CSR = 0.6, and for true CSR = 0.9 there were at least 490 non-convergent runs for each of the four scenarios.

**CONCLUSIONS**

The estimated clinical significance ratio decreased with increasing CSR, assuming the presence of a covariate.

In the absence of a clearly defined clinical significance for the reduction in IIV with statistical significance, may provide an indication of the presence of a covariate effect, with the magnitude of the reduction in IV indicative of the size of the CSR.

As expected based on the statistical properties of the covariate submodel, higher CSS was associated with a greater reduction in %IIV for the covariate parameter. In the examples studied, higher CSS also resulted in reduced variability in the estimated CSR. Reduction in IV was generally consistent with statistical significance.