Subjective endpoint clinical trials, such as analgesic investigations, are vulnerable to research site level variability. All sites collect and process data with their own nuances, which in the aggregate can lead to a reduced standardized effect size (SES) and consequently a false negative result. Systematic reviews have shown that increasing number of trial sites can often increase the risk of study failure. Clinical studies on analgesics targeting the treatment of acute pain often fail to statistically differentiate active drug from placebo, despite presumed efficacy of the study product in question. These type 2 errors may be secondary to decreased assay sensitivity in the multicenter environment for subjective endpoint clinical trials.

The standardized effect size (treatment effect/pooled standard deviation) is a reasonable measure of an investigator’s assay sensitivity. The assay sensitivity of an investigator is defined as the ability of a clinical trial to demonstrate a statistically significant difference between an active treatment and placebo if in fact such a difference exists. If the desired p value is held constant, the SES is inversely proportional to the square of the required n. Therefore, small changes in SES can translate into a significant impact on trial’s feasibility and its probability of success.

Hypothesis: We hypothesized that the SES generated in a single center environment (Lotus enrolled patients) would be significantly higher than the SES generated in the multicenter environment.

Methods
Lotus Clinical Research is a high-volume analgesic research testing unit that has recently been involved in multiple multicenter analgesic registration trials. In these studies, Lotus was able to enroll a significant portion of the total subject population which provided a unique opportunity to separate and analyze the data that were generated. Three multicenter randomized, double-blind, placebo-controlled pain studies in which Lotus enrolled a significant portion of the population were identified:

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- Abdominal Laparoscopy
- Hemorrhoidectomy
- Hernia Repair

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No. of Patients Enrolled</th>
<th>Average non-Lotus site</th>
<th>Total from all non-Lotus sites (# of sites)</th>
<th>Lotus non-Lotus effect size</th>
<th>% increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Laparoscopy</td>
<td>52</td>
<td>12</td>
<td>162 (16)</td>
<td>0.93</td>
<td>0.37</td>
</tr>
<tr>
<td>Hemorrhoidectomy</td>
<td>58</td>
<td>8.2</td>
<td>140 (17)</td>
<td>0.29</td>
<td>0.16</td>
</tr>
<tr>
<td>Hernia Repair</td>
<td>125</td>
<td>11.4</td>
<td>278 (24)</td>
<td>0.36</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Results
The pre-specified primary endpoints of three large multicenter pain studies were analyzed post-hoc to compare the standardized effect size (SES) of a single high enrolling center (Lotus) to the SES generated by all other sites in the aggregate.

In all three studies, the SES showed significant increases of 151%, 82%, and 64% compared to their respective non-Lotus data (see Table 1).

In each of the analgesic studies analyzed, Lotus enrolled between 30-46% of the investigation’s total required sample size. Since the SES is the key factor that drives the statistical power of an investigation, these increases suggest that reducing the number of centers in a subjective endpoint clinical trial may increase the ability of trials to effectively distinguish active drug from placebo (reduce the risk of a false negative result).

Conclusion
One paramount issue to improving the quality and efficiency of analgesic (subjective endpoint) research is the minimization of variability.

By utilizing as few centers as possible, one can more readily maintain highly skilled and consistent personnel which will ultimately reduce variability involved with data adjudication, collection and analysis.

Improving the quality and efficiency of clinical research may be better achieved by increasing enrollment rates at sites using strictly standardized research methods rather than attempting to disperse large numbers of subjects over multiple sites.

This trend has been observed repeatedly from multiple studies and should be an important consideration when planning analgesic trials.

References