Clustering historical controls for a continuous outcome in a Bayesian Phase II vulvodynia trial design

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Abstract: In a unique Phase II design, we seek to determine preliminary efficacy measures for a treatment of vulvodynia. We take as our efficacy endpoint the reduction in patient-reported pain after 4 weeks of treatment. Previous studies have shown a substantial placebo effect in this population, so the sample size required for detecting a significant effect using a binary efficacy outcome in a classical non-Bayesian framework is substantial. Our continuous pain reduction outcome improves the power we have to detect a significant treatment effect. Additionally, by using a Bayesian adaptive Phase II design with partial borrowing from historical controls, we can reduce the proportion of subjects randomized to the contemporaneous control group. However, not all historical controls will be equally relevant to the current comparison: some may be affected by unmeasured confounders that differ significantly across patients due to changes in cultural norms and current standards of care. Clustering the historical controls with the new data, we adaptively weight historical controls in the same cluster as the current data more than historical data in other, unmatching clusters. We conduct simulation studies to evaluate the operating characteristics of this design under different degrees of agreement between historical and contemporaneous subjects. Our results suggest Bayesian adaptive designs that borrow both cautiously and differentially among the historical controls can lead to vulvodynia trial designs that are both statistically and ethically attractive.