Challenge of Conducting a Multicenter Clinical Trial: Experience in Commencing a Vulvodynia Research Protocol

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RANDOMIZED CONTROLLED TRIALS (RCTs) are widely accepted as the gold standard for guiding clinical practice, but anticipated and unanticipated challenges may plague these trials. The Gabapentin (GABA) Group is a multicenter, multiple principle investigator (PI) clinical trial group funded by the National Institute of Child Health and Human Development (NICHD) and Office of Research on Women's Health (ORWH). We describe the challenges encountered in implementing an RCT on a pharmacologic intervention for the treatment of vulvodynia, a cause of chronic dyspareunia. These implementation hurdles likely reflect common themes experienced in many multicenter RCT's, but are often accentuated in studies involving women, where outcome measures are frequently less studied and more complex.¹ The National Institutes of Health (NIH) recently recognized the enormity of conducting multicenter trials and established clinical trial planning grants^{2,3} to support investigators in establishing research teams, developing data management tools, defining recruitment strategies, developing clinical protocols, and preparing operation manuals.

Many of the factors contributing to delays in study implementation of a multicenter trial are anticipated, such as group consensus on final protocol and operations, challenges that are not found in single-center single-PI grant mechanisms. In addition, protocols that incorporate more innovative and untested measures also present unique challenges. In our study, development of research equipment to measure pelvic pain thresholds required additional site visits and video conferences to train investigators and research staff and to establish inter-rater reliability. Manufacture of capsaicin to improve accuracy as a human pain model also required increased time and resources, including indemnification contractual agreements to transport capsaicin injections to the other two sites. Finally, the use of less common outcome measures required development of data entry forms not typically used in database systems.

One major hurdle was having multiple institutional review board (IRBs) review the same protocol, which added to delays in both protocol and amendment approvals.⁴ A unique delay was created by required notification to each IRB and Data Safety Monitoring Board (DSMB) when new data placed the intervention drug on the U.S. Food and Drug Administration

watch list. Because there is no written acknowledgement of investigational new drug approval for the study drug, further delay was encountered. These and many other concerns are noted by the Department of Health and Human Services' recent call for public comment on the need to revise human subjects' research guidelines.⁵

Although conflicts of interest (COI) are potentially found in all RCTs, they are magnified in multicenter trials. Even though our DSMB Committee and all co-investigators did not have any COIs prior to their invitation to our study, potential conflicts arose during the study, requiring study and DSMB membership restructuring.

We believe that many of these issues would have been ameliorated in our study if:

1. A working administrative relationship between centers was established at an early stage.
2. Additional time was built into the time line to accommodate the employment of new equipment, procedures, and database systems.
3. Coordinated IRB activity was commenced at study initiation and a determination was made regarding whether the coordinating center IRB or a central IRB could assume regulatory responsibilities.
4. Potential COIs were identified to prevent restructuring of DSMB and research team members after study initiation.

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Disclosure Statement

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