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Tyler W. Buckner, University of Colorado
Michael Wang, University of Colorado
David L. Cooper, Novo Nordisk Inc.
Neeraj N. Iyer, Novo Nordisk Inc.
Christine Kempton, Emory University

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Tyler W Buckner, Michael Wang, David L Cooper, Neeraj N Iyer, Christine L Kempton

1Hemophilia and Thrombosis Center, University of Colorado School of Medicine, Aurora, CO, 2Novo Nordisk Inc., Clinical, Medical, and Regulatory Affairs, Plainsboro, NJ, 3Departments of Pediatrics and Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA, USA

Background: The Pain, Functional Impairment, and Quality of Life (P-FiQ) study was an observational, cross-sectional assessment of the impact of pain on functional impairment and quality of life in adults with hemophilia in the United States who experience joint pain or bleeding. Objective: To describe known-groups validity of assessment tools used in the P-FiQ study. Patients and methods: Participants completed 5 patient-reported outcome (PRO) instruments (5-level EuroQoL 5-dimensional questionnaire [EQ-5D-5L] with visual analog scale [VAS], Brief Pain Inventory v2 Short Form [BPI], International Physical Activity Questionnaire [IPAQ], Short-Form Health Survey [SF-36v2], and Hemophilia Activities List [HAL]) and underwent a musculoskeletal examination (Hemophilia Joint Health Score [HJHS]) during a routine clinical visit. Results: P-FiQ enrolled 381 adults with hemophilia (median age, 34 years). Participants were predominantly white/non-Hispanic (69.2%), 75% had congenital hemophilia A, and 70.5% had severe hemophilia. Most (n=310) reported bleeding within the past 6 months (mean [SD] number of bleeds, 7.1 [13.00]). All instruments discriminated between relevant known (site- or self-reported) participant groups. Domains related to pain on EQ-5D-5L, BPI, and SF-36v2 discriminated self-reported pain (acute/chronic/both; \(P<0.05\)), domains related to functional impairment on IPAQ, SF-36v2, and HAL discriminated self-reported functional impairment (restricted/unrestricted; \(P<0.05\)), and domains related to mental health on the EQ-5D-5L and SF-36v2 discriminated self-reported anxiety/depression (yes/no; \(P<0.01\)). HJHS ankle and global gait domains and global score discriminated self-reported arthritis/bone/joint problems, percentage of lifetime on prophylaxis, current treatment regimen, and hemophilia severity (\(P<0.01\)); knee and elbow domains discriminated all of these (\(P<0.01\)) except for current treatment regimen. Conclusion: All assessment tools demonstrated known-group validity and may have practical applicability in evaluating adults with hemophilia in clinical and research settings in the United States. Keywords: hemophilia, pain, functional impairment, quality of life, patient-reported outcome, joint health

Introduction

Hemophilia is a rare X-linked congenital bleeding disorder that affects an estimated 20,000 people in the United States1 and 400,000 people worldwide.2 Improvements in
hemophilia care over the past 40 years have allowed people with hemophilia (PWH) to live longer, resulting in an increasing prevalence of hemophilia-related and age-related medical problems such as hemophilic arthropathy, a painful, deforming condition that arises from recurrent bleeding into the joints.\textsuperscript{3,4} Longitudinal data (1998–2011) from the Centers for Disease Control and Prevention (CDC)/US hemophilia treatment center network Universal Data Collection (UDC) database confirm that pain and physical limitations increase with age and disease severity, with 68.8% of adults with severe hemophilia who were born before 1958 reporting limitations to their overall activity level.\textsuperscript{5} Moreover, data from the multinational Hemophilia Experiences, Results, and Opportunities (HERO) study showed that a majority of the adult PWH surveyed (N=675) experienced pain and functional impairment, with 75% reporting moderate or extreme pain or discomfort, 59% reporting limited mobility at the time of the survey, and 89% reporting that pain had interfered with their daily activities within the month preceding the survey.\textsuperscript{6} A variety of generic and disease-specific patient-reported outcome (PRO) instruments and objective assessment tools have been used in studies of PWH to assess pain and functional impairment, but few have been assessed for reliability and content/construct validity in the US adult PWH population. Promising PRO instruments previously employed in clinical studies conducted in PWH include the Short-Form Health Survey (SF-36),\textsuperscript{10–12} the EuroQol 5-dimensional questionnaire (EQ-5D) with new 5-level response choices,\textsuperscript{6,10,11} the Brief Pain Inventory,\textsuperscript{14,15} the International Physical Activity Questionnaire (IPAQ),\textsuperscript{10} and the disease-specific Hemophilia Activities List (HAL), which arose out of semistructured interviews of PWH to assess activities affected by hemophilic arthropathy.\textsuperscript{16} The Hemophilia Joint Health Score (HJHS) was developed by the International Prophylaxis Study Group and initially was determined to have acceptable test–retest reliability and validity for use in assessing early joint progression in children with hemophilia.\textsuperscript{17} This instrument has been applied to assessment of adult PWH; however, it has not been tested for reliability or validity in the adult PWH population.

The Pain, Functional Impairment, and Quality of Life (P-FiQ) study aimed to assess the impact of pain on functional impairment and health-related quality of life (HRQoL) in adult PWH in the United States of any severity who experience joint pain or bleeding. Analysis of self-reported prevalence, description, and management of pain has been reported previously.\textsuperscript{18} A secondary objective of the study was to assess reliability and validity of the 5 general and disease-specific PRO instruments (5-level EQ-5D [EQ-5D-5L], Brief Pain Inventory v2 Short Form [BPI], IPAQ, SF-36v2, and HAL) and objective joint assessment tool (HJHS) used. The current report describes the known-group validity of the PRO instruments and HJHS in adult PWH. Internal consistency, item-total correlation, test–retest reliability, and convergent and discriminant validity were also evaluated as secondary objectives and are presented separately within this thematic series.

**Patients and methods**

**Study design**

The P-FiQ study (NCT01988532) was an observational, cross-sectional assessment of the impact of pain on functional impairment and HRQoL in adult PWH. Adult (≥18 years) male PWH of any severity with or without inhibitors and with a history of joint pain or joint bleeding completed 5 PRO instruments (EQ-5D-5L, BPI, IPAQ, SF-36v2, and HAL) and underwent an optional physical therapist-administered musculoskeletal examination (HJHS) at a routine comprehensive care visit. Initial subjects were eligible to participate in a retest cohort and completed the PRO instruments again at the end of their visit (~3–4 hours later). The study enrolled participants at 15 US sites between October 2013 and October 2014. Written informed consent was obtained from each participant, and the study protocol was approved by each local or central institutional review board (IRB; refer to Table S1 for a list of all approving IRBs). All surveys were conducted in English.

**Known groups and PRO and HJHS scales**

Known groups of interest were based on 6 self-reported characteristics (presence of anxiety or depression, type of pain, lifetime extent of routine [prophylactic] factor infusion, level of functional impairment, presence of arthritis/joint problems, and current treatment regimen) and 1 site-reported characteristic (hemophilia severity) (Table 1).

The EQ-5D-5L\textsuperscript{19} included an assessment of current (“today”) HRQoL across 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Scores for anxiety/depression and pain/discomfort were compared with known anxiety/depression, pain, percentage of lifetime on prophylaxis, and current treatment regimen groups.

The BPI\textsuperscript{20} was used to evaluate 4 pain severity items (worst, least, average, and current pain) and 7 pain interference items (effects on general activity, mood, walking
ability, normal work, relations with other people, sleep, and enjoyment of life), as experienced over the past week. Each BPI pain severity item, as well as the overall pain interference domain score, was compared with known pain, functional impairment, percentage of lifetime on prophylaxis, and current treatment regimen groups.

The IPAQ short form was used to measure levels of physical activity performed in the week prior to the visit. Participants provided the time (duration and frequency) spent walking as well as engaging in moderate intensity and vigorous intensity activities, which were used to determine weighted estimates of total activity per week (in metabolic equivalents of task [MET]-min/week). Participants reporting no physical activity in the prior week were excluded from MET analyses. Categorical activity levels (vigorous vs moderate/low) were derived from published methods.

Walking and moderate and vigorous intensity activity scores, as well as total activity scores, were compared with known functional impairment, arthritis/bone/joint problems, percentage of lifetime on prophylaxis, and current treatment regimen groups.

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Walking and moderate and vigorous intensity activity scores, as well as total activity scores, were compared with known functional impairment, arthritis/bone/joint problems, percentage of lifetime on prophylaxis, and current treatment regimen groups.
Known-group validity assessments of the EQ-5D-5L are summarized in Table 2. The anxiety/depression domain of the EQ-5D-5L discriminated self-reported anxiety/depression (yes vs no) groups, and the pain/discomfort domain discriminated self-reported pain type (acute vs chronic vs both) and lifetime extent of routine (prophylactic) factor infusion (never vs 25%–49% vs 50%–74% vs 75%–99% vs always) groups.

**BPI**

Known-group validity assessments of the BPI are summarized in Table 3. All 4 BPI severity items (worst pain, least pain, average pain, and current pain) discriminated self-reported pain type groups (acute vs chronic vs both). Additionally, the BPI pain interference summary score discriminated self-reported functional impairment groups (unrestricted/full activity vs limited/no activity).

**IPAQ**

Known-group validity assessments of the IPAQ are summarized in Table 4. On IPAQ, walking discriminated self-reported lifetime extent of routine (prophylactic) factor infusion groups (never vs 25%–49% vs 50%–74% vs 75%–99% vs always), and both moderate and vigorous activity discriminated those with self-reported arthritis/bone/joint problems (yes vs no). Additionally, IPAQ total activity (METs/week) discriminated self-reported functional impairment (unrestricted/full activity vs limited/no activity), arthritis/bone/joint problems (yes vs no), and current treatment regimen (on-demand for bleeds only vs routine prophylaxis with factor to prevent bleeding) groups.

**SF-36v2**

Known-group validity assessments of the SF-36v2 are summarized in Table 5. The PF domain discriminated self-reported functional impairment (unrestricted/full activity vs limited/no activity) and lifetime extent of routine (prophylactic) factor infusion (never vs 25%–49% vs 50%–74% vs 75%–99% vs always) groups. The BP domain discriminated self-reported pain type (acute vs chronic vs both) and lifetime extent of routine (prophylactic) factor infusion (never vs 25%–49% vs 50%–74% vs 75%–99% vs always) groups. The MH domain discriminated self-reported anxiety/depression groups (yes vs no).

**HAL**

Known-group validity assessments of the HAL are summarized in Table 6. Within the use of transportation domain, many respondents indicated that some of the specific items were not personally applicable (using public transportation, 40.7%; riding a bicycle, 28.6%). All HAL domains and scores discriminated self-reported functional impairment (unrestricted/full activity vs limited/no activity) and lifetime extent of routine (prophylactic) factor infusion (never vs 25%–49% vs 50%–74% vs 75%–99% vs always) groups.
Known-group validity of PRO instruments and HJHS in hemophilia

Table 4 Known-group validity: IPAQ

<table>
<thead>
<tr>
<th>IPAQ item</th>
<th>Self-reported functional impairment</th>
<th>Self-reported arthritis/bone/joint problems</th>
<th>Self-reported lifetime % on prophylaxis</th>
<th>Self-reported current treatment regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking</td>
<td>0.674</td>
<td>0.801</td>
<td>0.016</td>
<td>0.056</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.054</td>
<td>0.014</td>
<td>0.404</td>
<td>0.103</td>
</tr>
<tr>
<td>Vigorous</td>
<td>0.497</td>
<td>0.010</td>
<td>0.912</td>
<td>0.051</td>
</tr>
<tr>
<td>IPAQ score</td>
<td>Total activity</td>
<td>0.013</td>
<td>0.014</td>
<td>0.484</td>
</tr>
</tbody>
</table>

Notes: *Wilcoxon rank sum test, P-values shown; †unrestricted/full activity or limited/no activity; ‡yes or no; §never, 25%–49%, 50%–74%, 75%–99%, or always; and ‡on-demand or prophylaxis. Bold values indicate P-values < 0.05.

Abbreviation: IPAQ, International Physical Activity Questionnaire.

Discussion

This known-group validity analysis of the 5 PRO instruments and the HJHS support construct validity of the instruments by discriminating between groups of adult PWH with known characteristics thematically linked to each PRO item or domain. These findings, together with the results of reliability analyses (internal consistency, item-total correlation, and test-retest)24,25 and convergent and discriminant analyses,26 support the more widespread use of these PRO instruments and the HJHS in adult PWH in clinical and research settings.

As expected, known-group validity was observed in the current analysis when looking specifically at PRO items/domains related to a specific HRQoL theme. For example, domains related to pain on the EQ-5D-5L, BPI, and SF-36v2 discriminated between subjects with self-reported acute pain, chronic pain, or both (P < 0.05); domains related to functional impairment on IPAQ, SF-36v2, and HAL discriminated between subjects with restricted or unrestricted function (P < 0.05); and domains related to mental health on the EQ-5D-5L and SF-36v2 discriminated between subjects with and without anxiety/depression (P < 0.01). Furthermore, all of the HJHS domains and the global score were shown to discriminate those with self-reported arthritis/bone/joint problems.

However, while the study also assessed known-group validity based on PRO item/domain discrimination of treatment regimen characteristics (both on-demand vs prophylaxis and lifetime extent on prophylaxis), the results were less consistent. This finding likely reflects that the current treatment regimen may be a marker of bleeding phenotype or hemophilic arthropathy in the adult PWH population. For example, while adults with significant joint bleeding or

Table 5 Known-group validity: SF-36v2

<table>
<thead>
<tr>
<th>SF-36v2 item</th>
<th>Self-reported functional impairment</th>
<th>Self-reported pain</th>
<th>Self-reported anxiety/depression</th>
<th>Self-reported lifetime % on prophylaxis</th>
<th>Self-reported current treatment regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>&lt;0.0001</td>
<td>NE</td>
<td>NE</td>
<td>0.001</td>
<td>0.440</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>NE</td>
<td>&lt;0.0001</td>
<td>NE</td>
<td>0.004</td>
<td>0.791</td>
</tr>
<tr>
<td>Mental health</td>
<td>NE</td>
<td>NE</td>
<td>&lt;0.0001</td>
<td>0.070</td>
<td>0.810</td>
</tr>
</tbody>
</table>

Notes: *Wilcoxon rank sum test, P-values shown; †unrestricted/full activity or limited/no activity; ‡acute, chronic, or both; ‡yes or no; §never, 25%–49%, 50%–74%, 75%–99%, or always; ‡on-demand or prophylaxis. Bold values indicate P-values < 0.05.

Abbreviations: NE, not evaluated; SF-36v2, Short-Form Health Survey.
joint pain may experience arthropathy and reduced HRQoL, they may have chosen to start routine prophylactic factor infusions later in life to reduce bleeding and minimize pain. The extent of lifetime on routine prophylaxis is also more complicated in US adults who may not have been on primary prophylaxis since they were 1–2 years old (a more common treatment pattern in the United States since the late 1990s); therefore, the participant population within any of the categorical groups of lifetime on prophylaxis includes those who received prophylaxis early but stopped in adulthood, those who started only after joint bleeding and joint damage had occurred, and those who had periodically been on and off of prophylaxis.

Of note, the P-FiQ study was the first US hemophilia study to employ the 5-level version of the EQ-5D. Previous US studies conducted in PWH used the 3-level version, on which responses were limited to “no problems,” “some problems,” and “extreme problems.” The 5-level version includes more specific response levels (“no problems,” “slight problems,” “moderate problems,” “severe problems,” and “extreme problems”), resulting in greater discriminatory power and less susceptibility to ceiling effects. This might account for better discriminability of self-reported pain type (acute vs chronic vs both). Known-group validity in other EQ-5D-5L items may also be improved by the 5-level scoring.

In addition, the ability of the pain-specific BPI to discriminate between different pain types (acute vs chronic vs both) in adult PWH may derive from the specificity of the 4 pain severity items. In people with hemophilic arthropathy, ongoing cycles of inflammation resulting from joint bleeds (acute pain) occur in the context of chronic arthritic changes (chronic pain). Individuals with early arthropathy may experience predominantly joint bleed-related acute pain (lower least pain and average pain) that may be fully relieved by clotting factor alone, with or without the need for short-term

### Table 6 Known-group validity: HAL

<table>
<thead>
<tr>
<th>HAL item</th>
<th>Self-reported functional impairment</th>
<th>Self-reported lifetime % prophylaxis</th>
<th>Self-reported current treatment regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lying/sitting</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.3382</td>
</tr>
<tr>
<td>Leg function</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.1009</td>
</tr>
<tr>
<td>Arm function</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.5513</td>
</tr>
<tr>
<td>Transportation</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.8052</td>
</tr>
<tr>
<td>Self-care</td>
<td>&lt;0.0001</td>
<td></td>
<td>0.9587</td>
</tr>
<tr>
<td>Household tasks</td>
<td>&lt;0.0001</td>
<td></td>
<td>0.4658</td>
</tr>
<tr>
<td>Leisure/sports</td>
<td>&lt;0.0001</td>
<td></td>
<td>0.0163</td>
</tr>
<tr>
<td><strong>HAL scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper extremity activities</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.5396</td>
</tr>
<tr>
<td>Basic lower extremity activities</td>
<td>&lt;0.0001</td>
<td>&lt;0.0002</td>
<td>0.1335</td>
</tr>
<tr>
<td>Complex lower extremity activities</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0776</td>
</tr>
<tr>
<td>Global score</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.169</td>
</tr>
</tbody>
</table>

**Notes:** *Wilcoxon rank sum test, P-values shown; †unrestricted/full activity or limited/no activity; ‡never, 25%–49%, 50%–74%, 75%–99%, or always; ‡on-demand or prophylaxis. Bold values indicate P-values <0.05.

**Abbreviation:** HAL, Hemophilia Activities List.

### Table 7 Known-group validity: HJHS

<table>
<thead>
<tr>
<th>HJHS item</th>
<th>Self-reported arthritis/bone/joint problems</th>
<th>Self-reported lifetime % prophylaxis</th>
<th>Self-reported current treatment regimen</th>
<th>Site-reported hemophilia severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee</td>
<td>&lt;0.0001</td>
<td>0.002</td>
<td>0.9842</td>
<td>0.0018</td>
</tr>
<tr>
<td>Elbow</td>
<td>&lt;0.0001</td>
<td>0.0031</td>
<td>0.0939</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ankle</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Global gait</td>
<td>&lt;0.0001</td>
<td></td>
<td>0.0031</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>HJHS score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global score</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0072</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Notes:** *Wilcoxon rank sum test, P-values shown; †yes or no; ‡never, 25%–49%, 50%–74%, 75%–99%, or always; ‡on-demand or prophylaxis; ‡severe or mild/moderate. Bold values indicate P-values <0.05.

**Abbreviation:** HJHS, Hemophilia Joint Health Score.
use of analgesic medications. In contrast, those with chronic arthropathy may have more severe baseline pain in the non-bleeding state (higher least pain and average pain) that would be unlikely to improve with clotting factor alone and may require longer-term treatment with analgesic medications or non-pharmacologic pain therapies.

Of note, the HAL contained some items that were not widely relevant to the US PWH population studied; specifically, high numbers of subjects indicated that the transportation domain items “riding a bicycle” and “using public transportation” did not apply to them (28.6% and 40.7%, respectively). The HAL was developed and validated in Utrecht, the Netherlands, and thus the activities included reflect those relevant to the Dutch population. These items may therefore be more applicable in certain areas of the United States where these modes of transportation are most common (eg, urban areas). Despite this limitation, the discriminatory ability of the transportation domain was statistically significant ($P<0.0001$) for both functional impairment and lifetime extent of routine prophylaxis.

An important implication of these findings is that the IPAQ may have limited clinical utility among PWH who lead sedentary lifestyles (as a primary result of their native desire to engage in activity unrelated to hemophilia, restrictions suggested or imposed on them by parents or caregivers early in life, or limitations related directly to hemophilic arthropathy). Nearly half (45%) of the adult PWH surveyed in the P-FiQ study reported fewer than 10 minutes of physical activity per week. Among those who did report physical activity, moderate and vigorous activities were uncommon (~33% of active individuals reported participating in each), consistent with the low levels of physical activity previously observed among PWH. In the current analysis, the IPAQ total activity score was able to discriminate self-reported functional impairment ($P=0.013$) and arthritis/bone/joint problem ($P=0.014$) groups, although of the individual IPAQ activity scores (measured in MET-min/week), only moderate and vigorous activities (and not walking) discriminated self-reported arthritis/bone/joint problem groups ($P=0.014$ and $P=0.010$, respectively).

**Study limitations**

The P-FiQ study was designed primarily to assess the impact of pain on functional impairment and HRQoL in adult PWH in the United States who experience joint pain or bleeds, and validation of the study assessments was a secondary study objective. Certain design characteristics may therefore have influenced study outcomes. The study employed 5 PRO instruments comprising more than 100 questions, thus presenting the potential for respondent fatigue and associated response errors. However, test–retest reliability was acceptable and only the first response to the PRO instruments from each participant was used in this analysis. Additionally, subjects who were unable to complete the scales in English were excluded from study participation; therefore, the current findings may not be applicable to PWH in the United States who would be more comfortable completing the PRO instruments in another language. The inclusion criteria requiring participants to have had a history of joint pain or bleeding may also have biased the study population, and therefore reliability and validity assessments should not be assumed to apply to individuals with lower levels of joint damage.

**Conclusion**

All 5 PRO instruments and the HJHS demonstrated known-group validity by discriminating among patient characteristics of interest. These findings support the previously reported analyses of reliability (including test–retest) of these assessment tools in adult PWH.

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**Disclosure**

TW Buckner has served as a consultant to Baxalta, Genentech, and Novo Nordisk Inc. M Wang has served as a consultant to Baxalta, Biogen, CSL Behring, LFB, and Novo Nordisk Inc. DL Cooper and NN Iyer are employees of Novo Nordisk Inc. CL Kempton has served as a consultant to Baxalta, Biogen, CSL Behring, Hoffmann-La Roche, and Kedrion and received grant/research support from Novo Nordisk Inc. The authors report no other conflicts of interest in this work.
References


Supplementary material

Table S1 List of independent ethics committees/institutional review boards

1. Munson Medical Center, 1105 Sixth Street, Traverse City, MI 49684-2386
2. Emory University, 1599 Clifton Road, 5th Floor, Atlanta, GA 30322
3. St Vincent Hospital and Health Care Center, Inc., 8402 Harcourt Road, Suite 805, Indianapolis, IN 46260
4. Western Institutional Review Board, 3535 7th Avenue SW, Olympia, WA 98502-5010
5. Henry Ford Health System, CFP-Basement 046, 2799 West Grand Boulevard, Detroit, MI 48202-2689. Chairperson: Dr Timothy Roehrs, PhD
6. Vanderbilt University, 504 Oxford House, Nashville, TN 37232-4315
7. Western Institutional Review Board, 1019 39th Avenue SE, Puyallup, WA 98374
8. University of Colorado Multiple, Institutional Review Board, 13001 E 17th Place, Building 500, Room N3214, Aurora, CO 80045
9. Michigan State University, Olds Hall, 408 West Circle Drive, #207, East Lansing, MI 48824, Chairperson: Dr Ashir Kumar
10. Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239-3098
11. University of Minnesota, D528 Mayo Memorial Building, 420 Delaware Street S.E., MMC 820, Minneapolis, MN 55455
12. Rush University Medical Center, 1653 West Congress Parkway, Chicago, IL 60612-3833
13. Wake Forest University Health Services, Medical Center Boulevard, Winston-Salem, NC 27157-1023
14. Georgetown University, 37th and O Streets, N.W., Washington, DC 20057