Future Research Needs Paper

Number 38

Treatment for Restless Legs Syndrome: Future Research Needs

Identification of Future Research Needs From Comparative Effectiveness Review No. 86

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The information in this report is intended to help health care researchers and funders of research make well-informed decisions in designing and funding research and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of scientific judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical research and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances.

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None of the investigators have any affiliation or financial involvement that conflicts with the material presented in this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

An important part of evidence reports is to not only synthesize the evidence, but also to identify the gaps in evidence that limited the ability to answer the systematic review questions. AHRQ supports EPCs to work with various stakeholders to identify and prioritize the future research that is needed by decisionmakers. This information is provided for researchers and funders of research in these Future Research Needs papers. These papers are made available for public comment and use and may be revised.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The evidence reports undergo public comment prior to their release as a final report.

We welcome comments on this Future Research Needs document. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Executive Summary

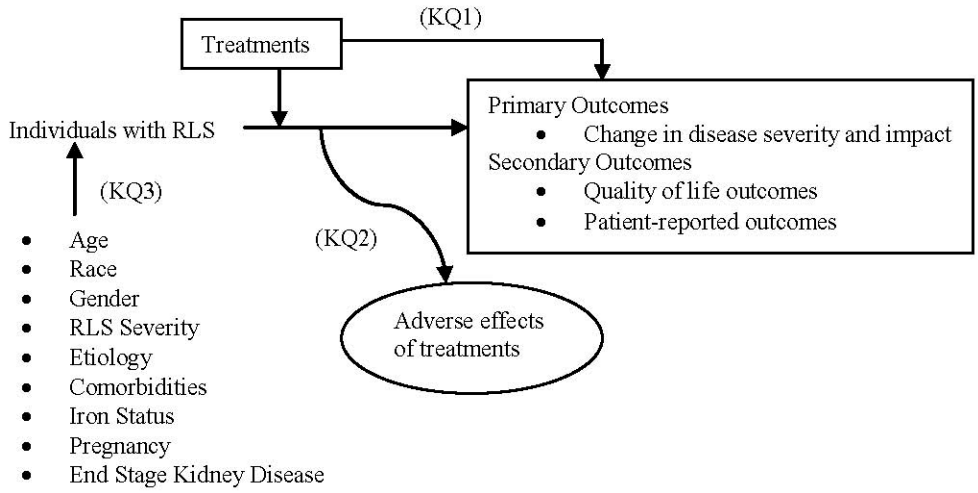
Background

This Future Research Needs (FRN) project is a followup to the draft Comparative Effectiveness Review (CER), "Treatment for Restless Legs Syndrome." The review was motivated by uncertainty around the effectiveness and comparative effectiveness of treatments for restless legs syndrome (RLS). The purpose of this FRN project is to identify and prioritize specific gaps in the current literature about the effectiveness and comparative effectiveness of treatments for RLS for which additional research would aid decisionmakers.

We used a deliberative process to identify evidence gaps, translate gaps into researchable questions, and solicit stakeholder opinion on the importance of research questions. This report proposes specific research needs along with research design considerations that may be useful in advancing the field.

The analytic framework adapted from the original draft CER (Figure A) describes the focus of the review. Research evaluated Key Questions (KQs) regarding treatment effectiveness and comparative effectiveness (KQ 1), long-term treatment tolerability, sustainability, and harms (KQ 2). We also assessed the impact of patient characteristics on the benefits and harms of treatment for RLS (KQ 3).[1]

Figure A. Analytic framework



Abbreviations: KQ = Key Question; RLS = restless legs syndrome.
Note: KQ 1: What is the comparative effectiveness of treatments for RLS?
KQ 2: What are the harms of RLS treatments?
KQ 3: What is the effect of patient characteristics on the benefits and harms of treatment for RLS?

The literature search conducted for the CER covered the bibliographic databases MEDLINE (via OVID), Embase, and Natural Standards through September 17, 2011. Our intent was to identify and synthesize data from relevant comparative effectiveness research on treatments for RLS.

For KQ 1 (What is the comparative effectiveness of treatment for RLS) authors of the CER found that randomized controlled trial (RCT) results were limited to short-term (<6 months) efficacy studies of active drugs versus placebo or usual care. Overall high-strength evidence showed that compared with placebo, dopamine agonists (ropinirole, pramipexole, and rotigotine)

reduced RLS symptoms, increased the percentage of patients with a clinically important response (defined as a ≥50 percent reduction in International Restless Legs Syndrome Study Group (IRLS) symptom scale scores or as a report of "improved" or "much improved" on patient or clinician-reported global impression scale) and improved disease-specific quality of life and patient-reported sleep outcomes. High-strength evidence showed that pregabalin increased the percentage of patients with a clinically important response (≥50 percent reduction in IRLS). Low-strength evidence demonstrated that calcium channel alpha-2-delta ligands improved clinician-reported global impression, disease-specific quality of life, and patient-reported sleep outcomes compared with placebo. Applicability was limited to nonpregnant, white, middle-aged adults with few comorbidities and RLS symptoms that were long term, frequent, and high-moderate to very severe.

As described in the full report, only three small RCTs addressed nonpharmacologic interventions. Pneumatic compression devices reduced IRLS symptom scale scores more than sham (moderate-strength evidence). Strength training and treadmill walking improved IRLS symptoms but adherence was poor and the study reported results only for completers. The botanical extract valerian was not effective. Evidence for both interventions was low strength.

No eligible studies assessed opioids, sedative hypnotics, or tramadol, though these are used for RLS treatment. One study found that the dopamine agonist cabergoline improved scores on the IRLS symptom scale and RLS quality of life scale more than levodopa (moderate-strength evidence). However, cabergoline is not approved for treatment of RLS and has limited use in the United States. Observational studies and long-term open-label followup from RCTs of pharmacologic interventions found that withdrawal from treatment at 1 year or more was common, ranging from 13 to 57 percent. Reasons for withdrawal included lack of efficacy (6 to 32 percent) and adverse events including augmentation (7 to 62 percent).

For KQ 2 (What are the harms of RLS treatments?), study withdrawals (due to any reason) from RCTs were slightly less common in patients randomized to dopaminergic agents than to placebo (moderate-strength evidence). Study withdrawals due to adverse effects were more common (though not statistically so) with dopamine agonist treatment than placebo (low-strength evidence). Differences were primarily due to an increase in withdrawals related to adverse effects (application site reactions) reported in three trials of transdermal rotigotine. More patients randomized to dopamine agonist had at least one adverse effect compared with placebo (high-strength evidence). Short-term adverse effects from treatment with dopamine agonists compared with placebo were nausea, vomiting, and somnolence (high-strength evidence for all these outcomes). Application site reactions were much more common with transdermal rotigotine than with placebo (high-strength evidence).

Some indirect evidence from placebo-controlled trials suggested that fatigue may be more common with ropinirole then pramipexole or rotigotine. Data from observation studies indicated that long-term augmentation ranged from 2.5 percent to 60 percent and varied markedly by type of dopamine agonist, followup time, study design, and method used to ascertain augmentation. No clear pattern explained this variability. Withdrawal from mostly dopamine agonist and levodopa treatment was common, occurring in 13 percent to 57 percent of subjects due either to lack of efficacy or adverse effects. Most studies reported treatment withdrawals greater than 20 percent at 1 year with adverse events including augmentation ranging from 7 to 62 percent.

For KQ 3 (What is the effect of patient characteristics on the benefits and harms of treatment for RLS?) the authors found that no RCTs examined the effect of patient or RLS characteristics on benefits and harms of treatments for primary RLS. No RCTs enrolled children or women who

were pregnant or recently postpartum, and nearly all specifically excluded these individuals. No eligible studies enrolled individuals with end-stage renal disease, and almost all specifically excluded these individuals. Two small randomized trials of iron therapy versus placebo in adults with iron deficiency provided low-strength evidence that iron may improve IRLS symptom scale scores and possibly the percentage of adults considered IRLS responders

Nearly all of the pharmacologic trials (dopamine agonist, calcium channel alpha-2-delta ligands, and iron therapies) were considered of good quality (having a low risk of bias). The applicability of the included evidence for RLS treatments is limited. Included studies were mostly short-term, placebo-controlled efficacy studies of dopamine agonists and calcium channel alpha-2-delta ligands conducted in a highly selected population of adults with moderate to very severe primary RLS of long-duration. Applicability to adults with less frequent or less severe (mild to moderate) RLS symptoms, children, or those with secondary RLS is unknown. Furthermore, randomized trials did not address long-term effectiveness, the comparative effectiveness and harms of commonly used treatments, or the effect of patient or RLS characteristics on outcomes.

Methods

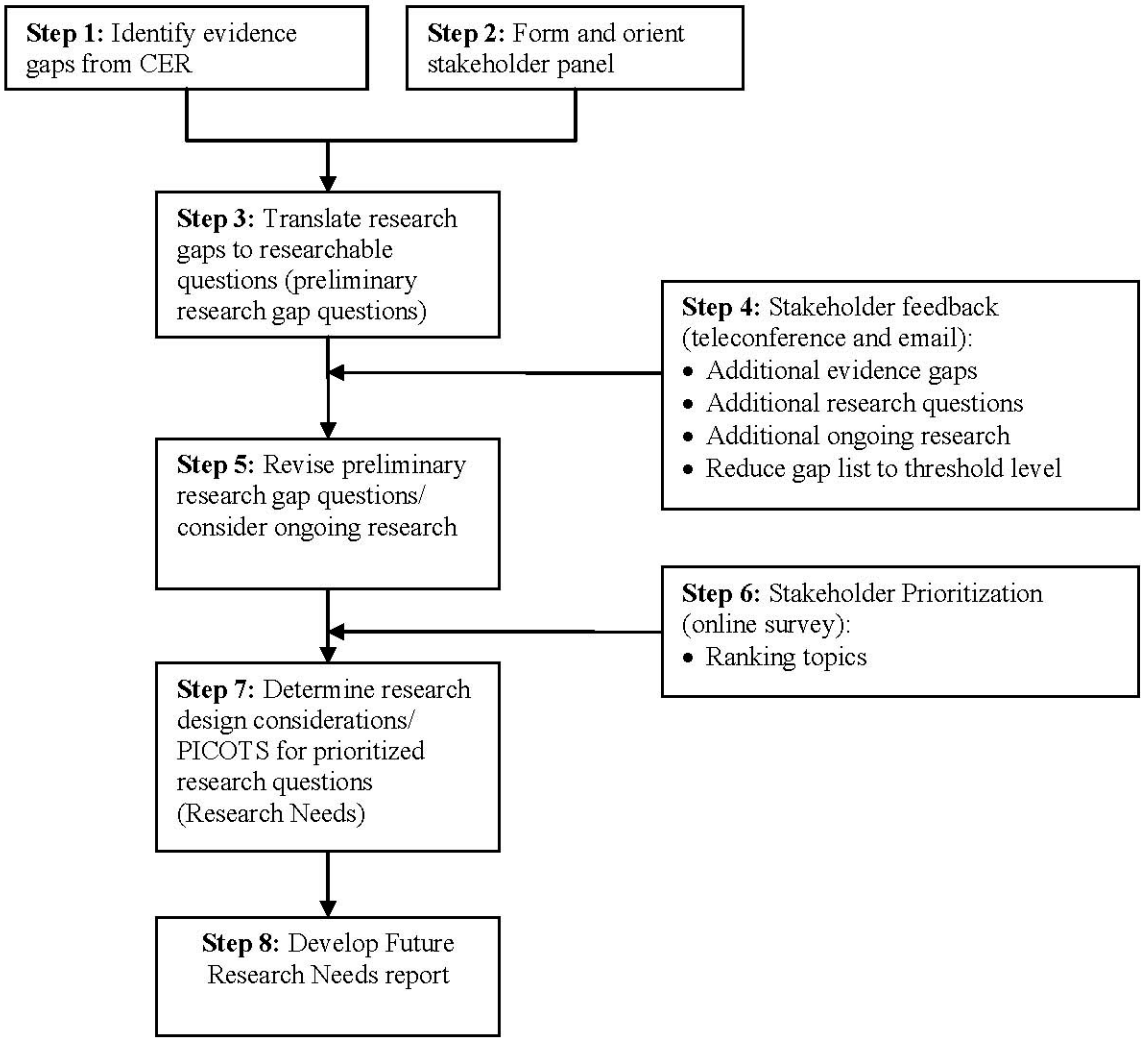
We used a deliberative process to identify and prioritize research questions relevant to the evidence gaps identified in the CER. Figure B illustrates the eight steps used to accomplish the objectives of this project.

First, research gaps identified in the CER were translated into research questions. Second, a diverse stakeholder panel with representation from various perspectives relevant to the topic was assembled. Research representatives were national experts familiar with evidence-based medicine and the obstacles faced in conducting well-designed research from the fields of neurology, psychology, and sleep medicine. Providers and consumers, including representation from the Restless Legs Syndrome Foundation, were also engaged because the decisional dilemmas faced by these groups are critical to identifying and prioritizing research questions.

We held a conference call with stakeholders to refine the original research gaps identified during the CER process. Based upon these conversations, we refined and added to our initial list of research gap questions. These are separated into categories (methodological research questions that need to be addressed to enhance the usefulness of current research, and topical research questions that have not been sufficiently addressed in the current literature). Because the stakeholders believed that some research questions that were considered out of scope from our review were critical to future comparative effectiveness research we elected to leave them in for prioritization processing. We sent the list of research questions to the stakeholders for ranking. Stakeholders numerically ranked their top three methodological research questions from a total of six and their top five topical research questions from a total of fourteen.

Rankings were weighted according to stakeholder numerical ordering of questions. Based on the natural breakpoints in these rankings, we determined high, moderate, and low priority research gap questions. High priority questions were deemed research needs. We then identified and discussed research design considerations for research needs.

Figure B. Project flow



Abbreviations: CER = Comparative Effectiveness Review; PICOTS = population, intervention, comparison, outcome, timing, setting.

Results

Prioritization Results

Discussions with stakeholders revealed their deep concern that the lack of basic understanding of RLS and how it works greatly impedes the potential for forward movement of research in the field. Therefore a number of questions were added to the prioritization process that are outside of the scope of the original CER, but that stakeholders felt were important earlier steps that would improve the ability to design and conduct research that will ultimately answer who would benefit from what RLS treatments. We analyzed weighted rankings for stakeholders participating in the Web-based prioritization process. From the seven stakeholders invited to rank research questions, six (86 percent) ranked both methodological and topical questions. We describe separately research needs that were within and outside the original CER scope.

Methodological Research Needs

Natural breakpoints in weighted rankings revealed two moderate-priority methodological research questions, one within the scope of the original CER and one outside of it. Because no methodological research question appeared to be of high priority, we considered the moderate-priority methodological research questions to be research needs. Addressing methodological research needs will improve the quality and enhance the clinical utility and translation of current and future research on treatments for RLS.

Within Scope:

- What are the minimum important differences in RLS outcome measures? Specifically
  - What IRLS scale scores (or changes in scores) translate to clinically meaningful improvement to assess for treatment effectiveness?
  - Is there a correlation between change in IRLS scale scores and clinically important change in Clinical Global Impression-if so what are those values?
  - What is the correlation of polysomnography outcomes to remission of symptoms?
  - What are the minimum outcomes to be reported?
  - What are the proportions of patients with remission of symptoms (IRLS score = 0), patient-reported sleep outcomes, quality of life, etc.?

Outside of Scope:

- What is the sensitivity and specificity of RLS diagnostic tools?

Considerations for Potential Research Designs

Methodological research needs could be addressed through a consensus development process (i.e., consensus conference), additional systematic reviews, epidemiological studies, diagnostic accuracy studies in targeted populations, and/or qualitative research.

Topical Research Needs

Topical research needs pertained to effectiveness and harms of treatments, clinical impact of RLS overall and in specific subgroups and areas to improve our understanding of RLS diagnosis and etiology. A natural breakpoint in weighted rankings of topical research questions revealed five research needs, two within the scope of the original CER and three outside of it. All topical research needs addressed the PICOTS (population, intervention, comparison, outcome, timing, setting) elements of populations and interventions. Addressing topical research needs will enhance understanding of efficacy and comparative effectiveness which was limited in the draft CER.

Within Scope:

- What are the short- and long-term comparative effectiveness and harms of treatments for RLS?
- Does tolerance/effectiveness of treatment for RLS vary by demographic/clinical/genetic factors?

Outside of Scope:

- What environmental factors are associated with RLS?
  - Is there a geographic/environmental predictor?
- What genetic linkages and biomarkers are associated with, diagnostic of, or causally linked to RLS?

- Is RLS associated with cardiovascular disease and other health conditions—in particular, what is the effect of RLS-related chronic sleep deprivation on cardiovascular health?

The draft CER, other reviews on the topic, current efficacy studies, and stakeholder discussions emphasized the need to address efficacy and comparative effectiveness for particular types of patients. While specific subgroups and interventions were not specified in this research need, subgroups can likely be defined by prevalent patient characteristics such as degree of symptoms, severity and etiology of disease, age, obesity, and other characteristics that appear to have an effect on response to treatment.

Considerations for Potential Research Designs

For each proposed research question, specific research designs are discussed in detail in the full text of this document. Some topical research needs are best addressed with experimental designs-randomized or controlled intervention trials. However, identifying specific patient subgroups whereby the effectiveness and harms of treatments may vary (hypothesis-generating research) may first be accomplished with less rigorous research designs (or from exploratory subgroup analyses in randomized trials). Additionally, understanding etiology, diagnostic criteria and prognosis is likely best first assessed by using high-quality prospective observational studies.

Observational studies and administrative databases could be used to extract hypothesized relationships between patient subgroups based on clinical characteristics, environmental factors and biomarkers and specific therapies or multimodal treatments. Hypotheses could be created through garnering expert opinion about which patient subgroups may respond differently to specific RLS therapies. However, this might be additionally addressed by evaluating subgroup findings from large randomized trials. A similar process could be used to identify specific intervention characteristics that contribute to effectiveness.

Once specific hypotheses are developed, they can be tested with experimental studies. RCTs are likely the best approach to comparing interventions. Sample size calculations should ensure adequate power to test selected predefined hypotheses and take any planned subgroup analyses into account. If sufficient subgroup sizes are not likely to be recruited, researchers may need to consider stratified recruitment to increase enrollment of these populations. Because RCTs often evaluate interventions in highly controlled settings within defined patient groups, they may not be fully applicable to broader populations seen in many (especially primary care) settings. Cohort studies and long-term extension of randomized trials would be of value in assessing long-term harms and treatment compliance particularly if including a broad spectrum of individuals and RLS severity.

Discussion

This FRN project refined and prioritized research needs relevant to the KQs addressed in the draft CER, "Treatment for Restless Legs Syndrome."[1] Additionally, questions were proposed that while outside the scope of the current CER, were identified as gaps in the body of literature that Stakeholders felt impedes the field greatly. Therefore, multiple gaps in evidence were identified that required future research to improve delivery of health care for patients identified with RLS.

We conducted a deliberative process to refine and expand research gaps identified in the CER through conversations with stakeholders with various perspectives of expertise on the topic. This process identified six methodological and fourteen topical research questions thought to

address identified evidence gaps. We then had stakeholders rank research questions. The highly ranked questions were deemed research needs. Stakeholders prioritized three methodological and five topical research needs.

Addressing methodological research needs will enhance the quality, clinical utility and comparability of future studies of RLS treatments. A common set of patient-centered and intermediate outcomes, with guidance on interpreting clinically important changes in outcomes scale scores will provide researchers with standardized and validated approaches to collecting outcomes data and determining effectiveness. Guidance on how RLS interventions should be defined in research studies and variables to report in studies as determined by a multidisciplinary panel will, when utilized, enhance the quality of research on the topic.

Advancement in the field needs to address which treatments for RLS are effective for which patients. In particular, our evidence report was intended to be a CER. Unfortunately, few studies directly compared treatments and indirect comparisons were not feasible due to differences in populations enrolled and the limited number of studies available. Additionally, a better understanding of the benefits and harms of treatment for RLS is essential to understanding their effectiveness. Testing specific hypothesis will fill specific evidence gaps identified and prioritized by our stakeholders.

While one strength of this project is the multidisciplinary perspective brought by broad stakeholder participation a larger sample of stakeholders would be useful. The stakeholders participating in this project represented various perspectives on treatments for RLS. However, the prioritized research needs reflect the opinions of these stakeholders and may not be generalizable to the population of stakeholders on this topic.

Conclusions

Addressing research needs identified in this FRN project will help create a broader and stronger evidence base in which clinical decisions can be made. Future research addressing specific research questions is likely to establish a preliminary research agenda on this topic. The highest priority research needs, both within the scope of the original CER and outside if it are summarized below:

Within Scope:

- What are the minimum important differences in RLS outcome measures? Specifically:
  - What IRLS scale scores (or changes in scores) translate to clinically meaningful improvement to assess for treatment effectiveness?
  - Is there a correlation between change in IRLS scale scores and clinically important change in Clinical Global Impression-if so what are those values?
  - What is the correlation of polysomnography outcomes to remission of symptoms?
  - What are the minimum outcomes to be reported?
  - What are the proportions of patients with remission of symptoms (IRLS score = 0), patient reported sleep outcomes, quality of life, etc.?
- What are the short- and long-term comparative effectiveness and harms of treatments for RLS?
- Does tolerance/effectiveness of treatment for RLS vary by demographic/clinical/genetic factors?

Outside of Scope:

- What is the sensitivity and specificity of RLS diagnostic tools?

- What environmental factors are associated with RLS?
  - Is there a geographic/environmental predictor?
- What genetic linkages and biomarkers are associated with, diagnostic of, or causally linked to RLS?
- Is RLS associated with cardiovascular disease and other health conditions-in particular what is the effect of RLS-related chronic sleep deprivation on cardiovascular health?

References

1. Wilt TJ, MacDonald R, Ouellette J, et al. Treatment for Restless Legs Syndrome. Comparative Effectiveness Review No. 86. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2007-10064-I.) AHRQ Publication No.12(13)-EHC147-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Background

Context

This Future Research Needs (FRN) project is a followup to the draft Comparative Effectiveness Review (CER), "Treatment for Restless Legs Syndrome."[1] The review was motivated by uncertainty around the effectiveness and comparative effectiveness of treatments for restless legs syndrome (RLS). FRN projects identify gaps in the current research that limit the conclusions in CERs and inform those who conduct and fund research of these gaps. FRN projects aim to encourage research likely to fill gaps and make the body of evidence more useful to decisionmakers. The report addressed the following Key Questions (KQs):

KQ 1. What is the comparative effectiveness of treatments for RLS?

a. What are the benefits from RLS treatments when compared with placebo or no treatment?
b. What are the benefits from RLS treatments when compared with other active treatments?
c. What is the durability and sustainability of treatment benefits?

KQ 2. What are the harms from RLS treatments?

a. What are the harms from RLS treatments when compared with placebo or no treatment?
b. What are the harms from RLS treatments when compared with other active treatments?
c. What are the long-term harms from treatment?

KQ 3. What is the effect of patient characteristics on the benefits and harms of treatment for RLS?

Restless Legs Syndrome

RLS is a neurological disorder characterized by unpleasant sensations in the legs and a distressing, irresistible urge to move them. The condition is defined and diagnosed based solely on clinical criteria. The essential diagnostic criteria for RLS were established by the International Restless Legs Syndrome Study Group (IRLS) in 1995[2] and revised in 2003.[3]

RLS symptoms are triggered by rest or inactivity and worsen at night. Movement such as walking, stretching, or bending the legs provides partial or complete relief. Yet, relief is temporary, and symptoms return when movement ceases.[4]

RLS encompasses a wide spectrum of symptom severity and frequency. Mild RLS may result in only minor annoyance, but severe RLS can interfere with work or social activities and reduce function and emotional well-being. RLS-induced sleep disruption may lead to poor daytime functioning, anxiety, and depression. Sleep deprivation and daytime fatigue are common reasons RLS patients seek treatment.[4]

Prevalence estimates for RLS in the United States range from 2.4 percent to 7.4 percent in adults.[5] The wide variation reflects different approaches to diagnosing RLS and defining its frequency and severity, and the fact that many RLS questionnaires do not account for individuals who have conditions with similar symptoms. One study designed to characterize the epidemiology of RLS in the U.S. population (a telephone survey of willing adults who answered

questions about RLS) defined RLS as "symptoms occurring at least twice weekly with moderate to severe impact" and found prevalence to be 1.5 percent.[3]

The etiology of primary RLS is unknown, but the disorder also occurs secondary to other conditions such as iron deficiency, end-stage renal disease, and pregnancy.[3] Compared with primary RLS, secondary RLS is less common, often starts later in life and progresses more rapidly, and tends to resolve when the underlying condition is treated or resolved.[3] Although mechanistic relationships are yet to be established, the pathophysiology of RLS may be closely linked to abnormalities in the dopaminergic system and iron metabolism.[4] The clinical course of RLS varies and commonly includes periods of remission, particularly in younger patients and those with milder disease. Severe RLS, however, is a chronic progressive disorder that may require long-term treatment.[4]

Treatments (nonpharmacologic and pharmacologic options) vary by patient age, comorbidities, preferences, and disease severity.[6] Nonpharmacologic options include: exercise, sleep hygiene, avoiding RLS precipitants (caffeine, alcohol, nicotine, antidepressants, antihistamines); counter stimulus to sensory symptoms (hot or cold baths, limb massage, compression stockings, counter-pulsation devices); herbal medicines and acupuncture; and cognitive behavioral therapy.

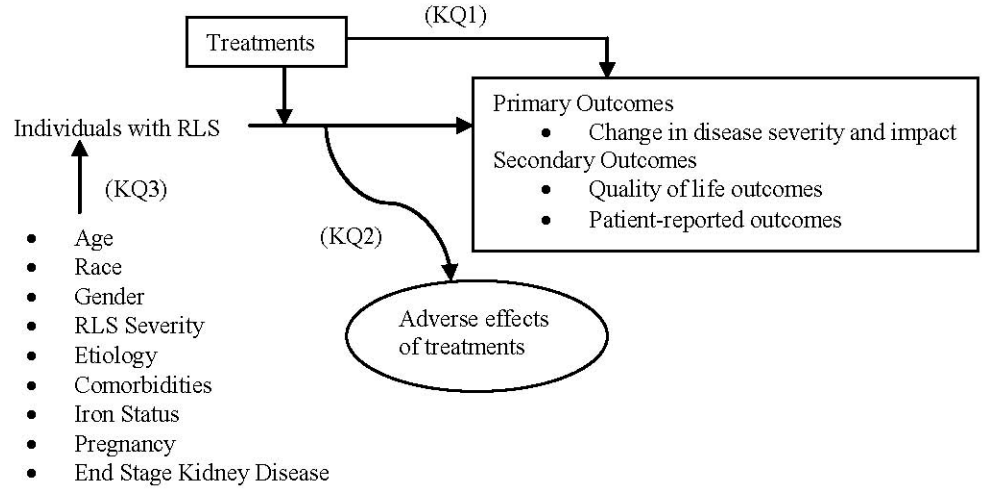
Pharmacologic treatment is generally reserved for patients with symptoms that are frequent (typically several times per week) and moderate to very severe. The major classes of drugs used are dopaminergic agents, sedative hypnotic agents, anticonvulsive agents, opiates, and iron. Of these, three dopamine agonists (pramipexole, ropinirole, and rotigotine) and one alpha-2-delta ligands anticonvulsant (gabapentin enacarbil) are U.S. Food and Drug Administration (FDA) approved for treatment of moderate to severe RLS.

A complication of long-term treatment with dopamine agonists is a drug-induced worsening of symptoms known as augmentation, characterized by greater symptom intensity, onset earlier in the day, and shorter latency during inactivity. With augmentation, symptoms may also spread to the arms, trunk, and face.[7]

The primary goal of RLS treatment is to reduce or eliminate symptoms and improve patient function, sleep, and quality of life. For patients with RLS believed secondary to other conditions (e.g., iron deficiency), treating the underlying condition first is recommended. RLS associated with pregnancy typically resolves postpartum; however, little is known about women with pregnancy-induced RLS whose symptoms persist after delivery.[8,9] The authors conducted a systematic review of the effectiveness and harms of treatments for restless leg syndrome with the primary intent to conduct a CER.

The analytic framework adapted from the original draft CER is shown in Figure 1.

Figure 1. Analytic framework



Abbreviations: KQ = Key Question; RLS = restless legs syndrome.
Note: KQ 1: What is the comparative effectiveness of treatments for RLS?
KQ 2: What are the harms of RLS treatments?
KQ 3: What is the effect of patient characteristics on the benefits and harms of treatment for RLS?

Findings of the Draft Comparative Effectiveness Review

The literature search conducted for the CER covered the bibliographic databases MEDLINE (via OVID), Embase, and Natural Standards, through September 17, 2011, in order to identify and synthesize data from relevant comparative effectiveness research on treatments for RLS. (Appendix B)

For KQ 1, authors of the draft CER found that randomized controlled trial (RCT) results were limited to short-term efficacy studies versus placebo or usual care (<6 months). Overall high-strength evidence showed that, compared with placebo, dopamine agonists (ropinirole, pramipexole, and rotigotine) reduced RLS symptoms, increased the percentage of patients with a clinically important response (≥50 percent reduction in International Restless Legs Syndrome symptom scale scores or who were "improved" or "much improved" on patient or clinician-reported global impression scale) and improved disease-specific quality of life and patient-reported sleep outcomes. High-strength evidence demonstrated that pregabalin increased the percentage of patients with a clinically important response (≥50 percent reduction in IRLS). Low-strength evidence showed that gamma-aminobutyric acid analogs improved clinician-reported global impression, disease-specific quality of life and patient-reported sleep outcomes compared with placebo. Applicability was limited to nonpregnant, white, middle-aged adults with few comorbidities and RLS symptoms that were long term, frequent, and high-moderate to very severe.

Only three small RCTs addressed nonpharmacologic interventions. (Complete references for these and other indicated studies are available in the full CER.) Pneumatic compression devices reduced IRLS symptom scale scores more than sham (moderate-strength evidence). Strength training and treadmill walking improved IRLS symptoms but adherence was poor and the studies reported results only for study completers. The botanical extract valerian was not effective. Evidence was low strength for all three interventions.

No eligible studies assessed opioids, sedative hypnotics, or tramadol, though these are used clinically for RLS treatment. One study found that the dopamine agonist cabergoline improved

scores on the IRLS symptom scale and RLS quality of life scale more than Levodopa (moderate-strength evidence). Carbergoline is not approved for treatment of RLS and has limited use in the United States due to increased risk for cardiac valvular disorders. Observational studies and long-term open-label followup from RCTs of pharmacologic interventions found that withdrawal from treatment at 1 year or more was common ranging from 13 to 57 percent. Reasons for withdrawal were lack of efficacy (6 to 32 percent), and adverse events including augmentation (7 to 62 percent).

For KQ 2, the authors found that study withdrawals (due to any reason) from RCTs were slightly less common in patients randomized to dopaminergic agents than to placebo (moderate-strength evidence). Study withdrawals due to adverse effects were more common (though not statistically so) with dopamine agonist treatment than placebo (low-strength evidence). Differences were primarily due to an increase in withdrawals related to adverse effects (application site reactions) reported in three trials of transdermal rotigotine. More patients randomized to dopamine agonist had at least one adverse effect compared with placebo (high-strength evidence). Short-term adverse effects from treatment with dopamine agonists compared with placebo were nausea, vomiting, and somnolence (high-strength evidence for all these outcomes). Application site reactions were much more common with transdermal rotigotine than with placebo (high-strength evidence).

Some indirect evidence from placebo-controlled trials suggests that fatigue may be more common with ropinirole then pramipexole or rotigotine. Data from observation studies indicates that long-term augmentation ranged from 2.5 percent to 60 percent and varied markedly by type of dopamine agonist, followup time, study design, and method used to ascertain augmentation. The authors found no clear pattern to explain this variability. Withdrawal from mostly dopamine agonist and levodopa treatment was common, occurring in 13 percent to 57 percent of subjects due either to lack of efficacy or adverse effects. Most studies reported treatment withdrawals greater than 20 percent at 1 year.

For KQ 3, the authors found that no RCTs examined the effect of patient or RLS characteristics on benefits and harms of treatments for primary RLS. No RCTs enrolled children or women who were pregnant or recently postpartum, and nearly all specifically excluded these individuals. No eligible studies enrolled individuals with end-stage renal disease, and almost all specifically excluded these individuals. Two small randomized trials of iron therapy versus placebo in adults with iron deficiency provided low-strength evidence that iron may improve IRLS symptom scale scores and possibly the percentage of adults considered IRLS responders.

Nearly all of the pharmacologic trials (dopamine agonist, anticonvulsants, and iron therapies) were considered of good quality (having a low risk of bias). The applicability of the included evidence for RLS treatments is limited. Included studies were mostly short-term, placebo-controlled efficacy studies of dopamine agonists and gamma-aminobutyric acid analogs conducted in a highly selected population of adults with moderate to very severe primary RLS of long-duration. Applicability to adults with less frequent or less severe (mild to moderate) RLS symptoms, children, or those with secondary RLS is unknown. Furthermore, studies did not address long-term effectiveness, the comparative effectiveness and harms of commonly used treatments, or the effect of patient or RLS characteristics on outcomes.

Objective

This FRNs project identifies and prioritizes specific gaps in the current literature on treatments for RLS that would, if addressed, assist decisionmakers. We used a deliberative

process to identify specific research needs along with research design considerations meant to advance the field.

Evidence Gaps and Research Question Development

As with much of the research on treatments for RLS, many studies of interventions for patients with RLS exhibited problems with design and conduct. Our original report included recommendations to improve future research on this topic. From the draft report we refined and developed the list of evidence gaps listed in the draft report and phrased the gaps as research questions. Discussion with stakeholders led to development of additional preliminary research questions (below). These are separated into two categories: (1) methodological research questions that need to be addressed to enhance the usefulness of current research, and (2) topical research questions that have not been sufficiently addressed within the current literature. Additionally, both recently published studies as well as on-going trials were considered when research gaps were identified (see Appendixes C and D).

Methodological Research Questions

1. What is the sensitivity/specificity of RLS diagnostic tools?
2. What is the effect of RLS-related chronic sleep deprivation on cardiovascular health?
3. What are the long-term consequences of RLS beyond currently understood sensory problems?
4. What is the causal pathway between RLS and insomnia?
5. What time frames should be studied to establish treatment benefits and harms?
6. Minimum important differences: (a) What IRLS scale score changes translate to clinically meaningful improvement for individual patients?; (b) Is there a correlation between change in IRLS and clinically important change in Clinical Global Impression?; (c) What is the correlation of polysomnography outcomes to remission of symptoms?; (d) What are the minimum outcomes to be reported?; (e)What are the proportions of patients with remission of symptoms (IRLS score = 0), patient reported sleep outcomes, quality of life, etc.?

Topical Research Questions

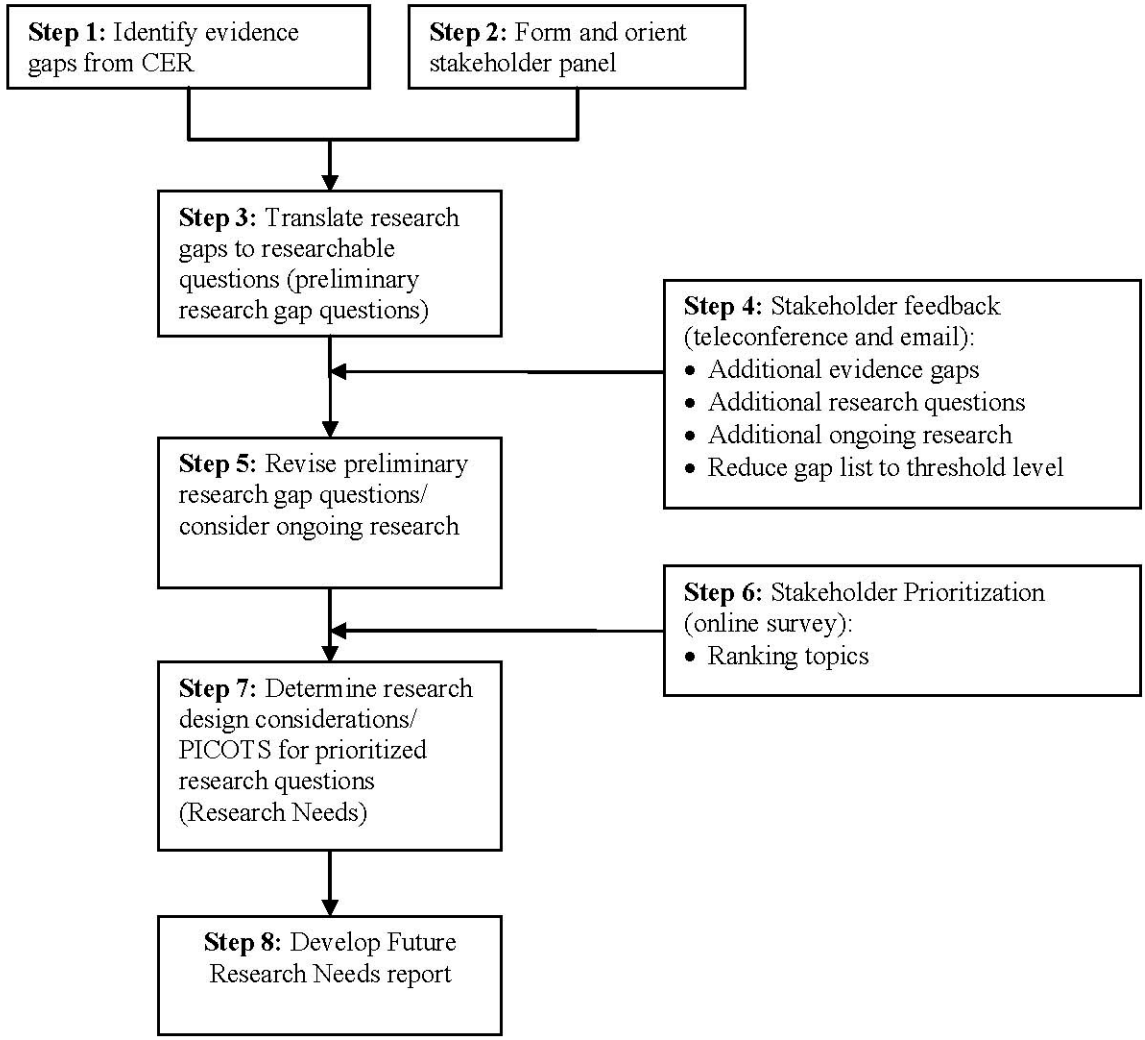
1. What environmental factors are associated with RLS? Is there a geographic/environmental predictor?
2. What are the genetic linkages and biomarkers that are associative or diagnostic or causally define RLS?
3. Does tolerance/effectiveness of treatment for RLS vary by demographic/clinical/genetic factors?
4. What is the short- and long-term comparative effectiveness and harms of treatments for RLS?
5. What is the long term effectiveness/comparative effectiveness of alpha 2 ligands for the treatment of RLS?
6. What is the effectiveness of nonpharmacologic therapies for RLS (mind-body, herbs/natural products, energy fields, and manipulation)?
7. How might the progression of RLS be delayed?
8. Does treatment of RLS improve non-RLS comorbidities?

9. Is RLS associated with cardiovascular disease and other health conditions—in particular what is the effect of RLS-related chronic sleep deprivation on cardiovascular health?
10. What is the effectiveness of other drugs that are not dopamine agonists or alpha 2 ligands (e.g., opioids and sedative hypnotics)?
11. Are certain patient characteristics (such as iron deficiency, disease duration, severity) more highly associated with augmentation with dopaminergic therapy?
12. Does treatment efficacy differ by RLS symptom severity?
13. What is the effectiveness of approved RLS drugs on patient subgroups such as children, older adults, and individuals with secondary RLS?
14. How do the findings from published randomized trials apply to patients diagnosed in primary care settings and/or with milder disease of shorter duration?

Methods

We used a deliberative process to identify and prioritize research questions relevant to the evidence gaps identified in the recently completed draft CER on treatments for RLS.[1] Figure 2 illustrates the eight steps used to accomplish the objectives of this project.

Figure 2. Project flow



Abbreviations: CER = Comparative Effectiveness Review; PICOTS = population, intervention, comparison, outcome, timing, setting.

Engagement of Stakeholders

We recruited a diverse panel of stakeholders with varied perspectives relevant to the topic. We followed guidance on stakeholder engagement for recruitment and communication.[10] We sought to recruit stakeholders who were actively interested in treatments for patients with RLS who wished to help shape future research priorities. We identified potential stakeholders via several means. We sought recommendations from the CER project team, including select Key Informants and Technical Expert Panel members. We also identified stakeholders who were serving on panels from related Agency for Healthcare Research and Quality (AHRQ) FRNs

projects or who were listed in the Effective Health Care Contacts Database.[11] Research representatives were national experts familiar with evidence-based medicine and aware of the obstacles faced in conducting well-designed research from neurology, psychology, and sleep medicine. Many stakeholders were also involved in the CER process as Key Informants, Technical Expert Panel members, or peer reviewers.

Handling Conflicts of Interest

We collected disclosures of conflicts of interests from all stakeholders. Disclosed interests did not bar any stakeholders from participation, but allowed the Evidence-based Practice Center (EPC) to evaluate contributions based upon possible conflicts. Stakeholders used a Web-based survey to rank specific topical research questions during the prioritization exercise, thus researchers and funders were blind to the stated opinions of one another.

Refinement of Research Questions

We provided members of our stakeholder panel with a preliminary set of research questions prior to our conference call. During the conference calls, we sought stakeholder input to further refine the research questions (i.e., organization and wording of the questions, identification of additional research questions, and elimination of research questions with limited clinical value). To facilitate this input, we provided stakeholders in advance with background material including the draft CER executive summary and the Effective Health Care Program Selection Criteria. We conducted several conference calls with available stakeholders in June of 2012. A total of seven stakeholders participated in the calls. All participants provided input on the calls. We circulated summaries of group calls to all participants. We invited stakeholders to clarify or supplement the call summaries or to suggest additional research questions in response to the call summaries, and several did so via email. We revised the preliminary questions based upon these discussions and email communications. The revised set of research questions for prioritization appears in Appendix A.

Prioritization

Our stakeholders were asked to prioritize these research questions according to specified criteria based on the potential impact of future research on that question. These criteria have been operationalized into seven components specific to EPC FRN projects. These components, called "Potential Value Criteria,"[11] are as follows:

- Potential for significant health impact on the current and future health status of people with respect to burden of the disease and health outcomes: mortality, morbidity and quality of life.
- Potential to reduce important inappropriate (or unexplained) variation in clinical practices known to relate to quality of care. Potential to resolve controversy or dilemmas in what constitutes appropriate health care. Potential to improve decisionmaking for patient or provider, by decreasing uncertainty.
- Potential for significant (nontrivial) economic impact related to the costs of health service: to reduce unnecessary or excessive costs; to reduce high costs due to high volume use; to reduce high costs due to high unit cost or aggregate cost. Costs may impact consumers, patients, health care systems, or payers.

- Potential risk from inaction: Unintended harms from lack of prioritization of proposed research; opportunity cost of inaction.
- Addresses inequities, vulnerable, diverse populations (including issues for patient subgroups); potential to reduce health inequities.
- Potential to allow assessment of ethical, legal, social issues pertaining to the condition.
- Potential for new knowledge: research would not be redundant; question not sufficiently researched, including completed and in-process research; utility of available evidence limited by changes in practice, e.g., disease detection or evolution in technology.

We then asked stakeholders to rank the research questions focusing on the Potential Impact criteria (i.e., the likelihood that addressing the research gap question would inform clinical practice and policy). We developed a Web-based survey using SurveyMonkey to collect stakeholder prioritization of the research gap questions.[12] All seven stakeholders were invited to rank research questions identified via the stakeholder conference calls. These stakeholders were asked to numerically rank their top three of six methodological research questions, and their top five of 14 topical research questions.

Stakeholder rankings were weighted according to their assigned numerical ranking. For the methodological questions, if a stakeholder assigned a question the number one ranking, that question received three points; number two ranking—two points; number three ranking—one point. For the topical questions, if a stakeholder assigned a question the number one ranking, that question received five points; number two ranking—four points; number three ranking—three points; number four ranking—two points; number five ranking—one point. We identified natural breakpoints in the weighted rankings that separated high-, moderate-, and low-priority research questions. Highly prioritized research questions were considered research needs. We disseminated results of the forced ranking procedure to all engaged stakeholders for review and comment prior to preparing the final report.

We then evaluated the feasibility criteria for research needs. We framed feasibility in terms of anticipated research designs. For example, factors that affect the feasibility of conducting randomized controlled trials include the sample size needed for the outcome, the size of the available pool of potential subjects, followup duration, willingness to randomize, and applicability issues. In contrast to randomization and applicability, observational studies face feasibility issues related to measuring study variables using different data sources and unobserved variables that create risk of bias.

Research Design Considerations

We generated research design considerations for identified research needs. For methodological research needs, we provided context and described resources and research design considerations potentially useful to researchers, facilitators, and funders of this type of research. For topical research needs, we highlighted the relevant PICOTS (population, intervention, comparison, outcome, timing, setting) element(s), provided context, described related ongoing research, and discussed potential research designs. Because more than one research design can be applied to an individual research need, we discussed the advantages and disadvantages of different options. We did not consult with stakeholders for input on research design considerations.

Results

Research Needs

Prioritization Results

Discussions with stakeholders revealed their deep concern that the lack of basic understanding of RLS and how it works greatly impedes the potential for forward movement of comparative effectiveness research in the field. Therefore a number of questions were added to the prioritization process that may be outside of the scope of the original CER, but that stakeholders felt were important earlier steps that would improve the ability to design and conduct research that will ultimately answer who would benefit from what RLS treatments. We analyzed weighted rankings for stakeholders participating in the Web-based prioritization process. From the seven stakeholders invited to rank research questions, six (86 percent) ranked both methodological and topical questions. We describe separately research needs that were within and outside the original CER scope.

Stakeholders separately ranked methodological and topical research questions (with no consideration of scope). A total of six of the seven stakeholders invited to participate in the ranking process ranked methodological and topical research questions. Participating stakeholders primarily identified themselves as physicians. We analyzed weighted stakeholder rankings for each research question to identify natural breakpoints (Table 1). High- and moderate-priority methodological research questions and high-priority topical research questions were deemed research needs.

Table 1. Stakeholder prioritization of research gap questions

Research Gap Questions		
Ranking	**Total (Points)**	**PICOTS Element**
Methodological Topics Needing Consensus (n=5)		
Tier 1: High Priority		
What are the minimum important differences: (a) What IRLS scale score changes translate to clinically meaningful improvement for individual patients?; (b) Is there a correlation between change in IRLS and clinically important change in Clinical Global Impression?; (c) What is the correlation of polysomnography outcomes to remission of symptoms?; (d) What are the minimum outcomes to be reported? (e) What are the proportions of patients with remission of symptoms (IRLS score = 0), patient reported sleep outcomes, quality of life, etc.?	8	C,O
What is the sensitivity/specificity of RLS diagnostic tools?	7	I
Tier 2: Moderate Priority		
What are the long-term consequences of RLS beyond currently understood sensory problems?	5	T
What time frames should be studied to establish treatment benefits and harms?	4	T

Table 1. Stakeholder prioritization of research gap questions (continued)

Tier 3: Low Priority		
What is the causal pathway between RLS and insomnia?	2	O
Topical Questions Needing Trials (n=15)		
Tier 1: High Priority		
What are the genetic linkages and biomarkers that are associative or diagnostic or causally define RLS?	17	P
What environmental factors are associated with RLS? Is there a geographic/environmental predictor?	12	P
What is the short- and long-term comparative effectiveness and harms of treatments for RLS?	12	C,T
Is RLS a risk factor for cardiovascular disease and other health conditions?	12	O
Does tolerance/effectiveness of treatment for RLS vary by demographic/clinical/genetic factors?	11	P
Tier 2: Moderate Priority		
What is the effect of RLS-related chronic sleep deprivation on cardiovascular health?	10	O
How might the progression of RLS be delayed?	6	O
What is the effectiveness of nonpharmacologic therapies for RLS? (mind-body, herbs/natural products, energy fields, and manipulation).	5	I
Are certain patient characteristics (iron deficiency or disease duration or severity more highly associated with augmentation with dopaminergic therapy?	4	P
Tier 3: Low Priority		
What is the long-term effectiveness/comparative effectiveness of alpha 2 ligands for the treatment of RLS?	3	I
Does treatment of RLS improve non-RLS comorbidities?	3	O
What is the effectiveness of other drugs that are not dopamine agonists or alpha 2 ligands (e.g., opioids and sedative hypnotics)?	2	I
Does treatment efficacy differ by RLS symptom severity?	2	I,O
What is the effectiveness of approved RLS drugs on patient subgroups such as children, older adults, and individuals with secondary RLS?	1	P
How do the findings from published randomized trials apply to patients diagnosed in primary care settings and/or with milder disease of shorter duration?	0	I,C

Abbreviations: PICOTS = population, intervention, comparison, outcome, timing, setting; RLS = restless legs syndrome.
Note: Stakeholder rankings were weighted according to their assigned numerical ranking. For the methodological questions, if a stakeholder assigned a question the number one ranking, that question received three points; number two ranking – two points; number three ranking – one point. For the topical questions, if a stakeholder assigned a question the number one ranking, that question received five points; number two ranking – four points; number three ranking – three points; number four ranking – two points; number five ranking – one point.

Methodological Research Needs

From among the methodological questions, stakeholders prioritized the identification of minimum important differences (within the scope of the CER) (with 50 percent of voters ranking it a priority) as well as the determination of the sensitivity/specificity of RLS diagnostic tools (outside of the scope of the CER) (Tier 1: High Priority), with 50 and 67 percent of stakeholders ranking them a priority respectively. The rankings of two additional methodological research gap questions were clustered together, but distantly less important to stakeholders than the top tier (Tier 2: Moderate Priority). Addressing methodological research needs will enhance the utility and translation of current and future research on treatments for RLS.

Within Scope:

- What are the minimum important differences in RLS outcome measures? Specifically
    - What IRLS scale scores (or changes in scores) translate to clinically meaningful improvement to assess for treatment effectiveness?
    - Is there a correlation between change in IRLS scale scores and clinically important change in Clinical Global Impression-if so what are those values?
    - What is the correlation of polysomnography outcomes to remission of symptoms?
    - What are the minimum outcomes to be reported?

- What are the proportions of patients with remission of symptoms (IRLS score = 0), patient-reported sleep outcomes, quality of life, etc.?

Outside of Scope:

- What is the sensitivity and specificity of RLS diagnostic tools?

Methodological research needs pertain to how effectiveness is measured and the consistency and completeness of research studies and reporting on treatments for RLS.

Considerations for Potential Research Designs

Methodological research needs could be addressed through a consensus development process (i.e., consensus conference), additional systematic reviews, epidemiological studies, and/or qualitative research.

Topical Research Needs

A natural breakpoint in weighted rankings of topical research questions revealed five research needs, two within the scope of the original CER and three outside of it. All topical research needs addressed the PICOTS elements of populations and interventions. Addressing identified topical research needs will enhance understanding of efficacy and comparative effectiveness, which was limited in the draft CER.

Within Scope:

- What are the short- and long-term comparative effectiveness and harms of treatments for RLS?
- Does tolerance/effectiveness of treatment for RLS vary by demographic/clinical/genetic factors?

Outside of Scope:

- What environmental factors are associated with RLS?
  - Is there a geographic/environmental predictor?
- What genetic linkages and biomarkers are associated with, diagnostic of, or causally linked to RLS?
- Is RLS associated with cardiovascular disease and other health conditions—in particular what is the effect of RLS-related chronic sleep deprivation on cardiovascular health?

The draft CER, other reviews on the topic, current efficacy studies, and stakeholder discussions emphasized the need to address efficacy and comparative effectiveness for particular types of patients. While specific subgroups and interventions were not specified in this research need, subgroups can likely be defined by prevalent patient characteristics such as degree of symptoms, severity of disease, age, obesity, and other characteristics that appear to have an effect on response to treatment.

Considerations for Potential Research Designs

Topical research needs would be best addressed with experimental designs (new randomized controlled trials for effectiveness and comparative effectiveness). However, identifying specific RLS patient subgroups based on environmental or genetic factors, or biomarkers (hypothesis

generating research) may first be accomplished with less rigorous research designs. Observational studies and administrative databases could be used to extract hypothesized relationships between patient subgroups based on clinical characteristics, environmental factors and biomarkers and specific therapies or multimodal treatments. Garnering expert opinion regarding which RLS patient subgroups may respond differently to specific therapies should also be considered to create hypotheses. A similar process could be used to identify specific intervention characteristics of RLS patients that contribute to effectiveness. Furthermore, assessing environmental and genetic linkages is more efficiently accomplished through case-control studies of individuals with RLS (primary or secondary) and appropriately matched controls without RLS.

Once specific hypotheses are developed, they can be tested with experimental studies. Randomized Controlled Trials (RCTs) are likely the best approach to comparing interventions. RCTs with sufficient sample sizes can detect meaningful differences in outcomes because randomization minimizes bias from both observed and unobserved (or unmeasured) variables, giving a clear picture of treatment effects in specific populations. Sample size calculations should insure adequate power to test hypotheses and take any planned subgroup analyses into account. If sufficient subgroup sizes are not likely to be recruited, researchers may need to consider stratified recruitment from these populations. RCTs are the research design most likely to produce valid conclusions about the efficacy or comparative effectiveness of treatments. However, because they evaluate interventions in controlled settings within defined patient groups, they do not always resemble real-world patients and settings.

Cohort studies are less resource intensive, easier to recruit patients to, and provide results with greater applicability than RCTs. Prospective cohort studies enroll and follow patients over time to assess outcomes. The advantages of cohort studies include having a comparison group without randomizing patients and having a sufficient number and variety of patients. This study design makes testing for subgroup effects more feasible given the greater variety of patient and condition characteristics (age, gender, comorbidities, etc.) and the larger sample sizes that are typically possible with cohort studies. Because prospective cohort studies can better study real-world practice as compared with RCTs, many different variations in intervention characteristics can be studied as long as the appropriate data is collected and sufficient samples of patients receiving particular intervention variations. As mentioned above, case-control studies of individuals with RLS (primary or secondary) and appropriately matched controls without RLS would be a preferred study design to assess environmental and genetic linkages.

Following patients over time and attrition is burdensome in cohort studies, as in RCTs, especially when long followup periods are required. However, the greatest disadvantage with cohort studies is the potential selection bias created by nonrandomization. Controlling for the effects of all known and unknown confounding variables is difficult to accomplish through matching and/or statistical techniques. These confounding variables may account for the specific treatments received and therefore also be responsible for differences in outcomes, rather than the treatments themselves. Because treatment selection biases can come from patient and provider factors, these need to be identified, measured, and adjusted for use in statistical analyses.

Tables 2 through 6 provide details on design considerations for each identified research need.

Potential Research Design Considerations for Questions Inside Scope

Table 2. Design considerations: What are the short- and long-term comparative effectiveness and harms of treatments for RLS?

Considerations	RCT	Prospective Observational Study
Design description	Individual patients randomly assigned to treatment programs.	Individuals select treatment program.
Population	Patients diagnosed with RLS.	Patients diagnosed with RLS.
Intervention	RLS treatment, including both drug therapies and nondrug therapies.	RLS treatment, including both drug therapies and nondrug therapies.
Comparator	Nontreatment, drugs, or nondrug therapies.	Nontreatment, drugs, or nondrug therapies.
Outcomes	Symptom abatement (remission), decreased IRLS scores, clinical responders on IRLS scale scores, CGI, measures of sleep quality and treatment satisfaction, adherence, tolerance, reported AEs or SAEs.	Symptom abatement (remission), decreased IRLS scores, clinical responders on IRLS scale scores, CGI, measures of sleep quality and treatment satisfaction, adherence, tolerance, reported AEs or SAEs.
Timing	For at least 6-12 months?	
Setting	Out-patient sleep medicine or neurology clinics.	Out-patient sleep medicine or neurology clinics.
Advantages for producing a valid result	This design, if feasible, will likely produce more valid results.	This design is more feasible than an RCT but will subject to confounding. Investigators should be careful to collect data necessary to control for known effect modifiers and confounders.
Resource use, size, and duration	RCTs are difficult to recruit to, require large sample sizes and are challenged by loss-to-follow-up.	Sample sizes will need to be large, and lost-to-follow-up issues will likely be significant.
Ethical, legal, and social issues	No ethical, legal or social issues exist.	No ethical, legal or social issues exist.
Availability of data/ ability to recruit	Poor. RCTs require significant time commitment; patients may be unwilling to leave treatment choice to randomization.	Fewer challenges to recruitment than with RCT.

Abbreviations: AE = adverse event; CGI = Clinical Global Impression; IRLS = International RLS Study Group; RCT = randomized controlled trial; RLS = restless legs syndrome; SAEs = serious adverse events.

Table 3. Design considerations: Does tolerance/effectiveness of treatment for RLS vary by demographic/clinical/genetic factors?

Considerations	Meta-Analysis of Published Data or Individual Participant Data	Prospective Observational Study
Design description	Systematic review of future published literature that seeks to determine if tolerance/effectiveness of treatment for RLS vary by demographic /clinical/genetic factors. Individual patient level meta-analysis or subgroup reporting from existing studies that includes key baseline demographic/clinical/genetic factors.	Prospective observational studies or post RCT open label continuation studies that assess long-term tolerance and effectiveness according to key demographic, clinical and genetic factors.
Population	Patients diagnosed with RLS receiving treatment.	Patients diagnosed with RLS receiving treatment.
Intervention	Treatment for RLS. (Both drug and nondrug treatment options could be considered.)	Treatment for RLS. (Both drug and nondrug treatment options could be considered.)
Comparator	Individuals with RLS.	Individuals with RLS.
Outcomes	Measures of drug tolerance and effectiveness according to baseline demographic/clinical and genetic factors including primary vs. secondary RLS. Outcomes would include: adherence, augmentation, treatment-related symptom. abatement, decreased IRLS scale scores, reported AEs or SAEs.	Baseline demographic information including clinical and genetic factors as well as treatment-related symptom abatement, decreased IRLS scores, reported AEs or SAEs.
Timing	At least 12 months.	At least 12 months.
Setting	Primary care clinics, Out-patient sleep medicine or neurology clinic.	Out-patient sleep medicine or neurology clinic.
Advantages for producing a valid result	Benefits of a potentially large sample size, no recruitment necessary with the disadvantages of pooling potentially varying patient populations.	This design is very feasible as treatment decision is determined by patient and provider, not by randomization.
Resource use, size, and duration	Resource use is less than an RCT or even an Observational study but would still require investigator and analysis time.	Resource use is likely higher than an meta-analysis but still smaller than a large full scale long-term RCT.
Ethical, legal, and social issues	No important ethical, legal or social issues.	No important ethical, legal or social issues.
Availability of data/ability to recruit	Fair.	Fair.

Abbreviations: AE = adverse event; IRLS = International RLS Study Group; RCT = randomized controlled trial; RLS = restless legs syndrome; SAEs = serious adverse events.

Potential Research Design Considerations for Questions Outside Scope

Table 4. Design considerations: What geographic/environmental factors are associated with RLS?

Considerations	Meta-Analysis of Existing Published Data and/or Prospective Observational Studies
Design description	Systematic review of the literature that seeks to determine if there are geographic or environmental factors similar across RLS populations. Population based studies to assess geographic and environmental factors at baseline and risk of development of RLS (prospective cohort and/or case-control studies).
Population	Patients with RLS (primary and secondary).
Intervention	RLS diagnosis.
Comparator	Matched controls (age, gender, race, comorbid conditions, socio-economic status etc.).
Outcomes	Odds ratios for RLS vs. controls associated with putative geographic, environmental factors.
Timing	NA
Setting	Population based.
Advantages for producing a valid result	Results will attempt to determine the existence of geographic or environmental factors that may be associated with either primary or secondary RLS.
Resource use, size, and duration	Modest: study might be able to be conducted using secondary data analysis of existing population based studies of individuals with and without RLS. Resource use includes significant investigator and analyst time and may require additional survey and data collection from existing cohorts.
Ethical, legal, and social issues	Little important ethical, legal, or social issues exist.
Availability of data/ability to recruit	Unknown, data will be limited to those studies that include demographic outcomes.

Abbreviations: NA = not available; RLS = restless legs syndrome.

Table 5. Design considerations: What genetic linkages/biomarkers are associative, diagnostic of, or causally define RLS?

Considerations	Meta-Analysis of Existing Data	Observational Study
Design description	Systematic review of the literature that seeks to determine if there are genetic linkages and biomarkers that are associative, diagnostic of, or causally define RLS.	Case-control studies of individuals diagnosed with RLS compared with appropriately matched controls (age, gender, comorbid conditions) would be enrolled regardless of treatment intentions. Studies should separately address individuals with primary and secondary RLS.
Population	Studies of RLS patients with baseline demographic data that include genetic and biomarker information.	Patients with an RLS diagnosis (primary and secondary).
Intervention	RLS diagnosis.	RLS diagnosis.
Comparator	Matched controls (age, gender, race, comorbidities.	Matched controls (e.g. age, gender, race, comorbidities).
Outcomes	Baseline demographic data to include genetic and biomarker information.	Genetic and biomarker information.
Timing	NA	NA
Setting	Population based studies, primary care or out-patient sleep medicine or neurology clinic.	Population based studies, primary care or out-patient sleep medicine or neurology clinic.
Advantages for producing a valid result	Results will attempt to determine the existence of genetic and biomarker predictors for RLS.	This design is very feasible as treatment decision is determined by patient and provider, not by randomization. Causality will be difficult to determine, but it is possible that associations between genetics and RLS diagnosis will be able to be seen with sufficient population size.
Resource use, size, and duration	Minimal, study can be conducted by secondary data analysis. Resource use includes significant investigator and analyst time.	Sample size will need to be large given the number of treatment options available. Pharmacoepidemiologic datasets may be of use to more efficiently address this.
Ethical, legal, and social issues	No important ethical, legal or social issues exist.	No important ethical, legal or social issues exist.
Availability of data/ability to recruit	Unknown, data will be limited to those studies that include genetic and biomarker outcomes.	Modest challenges to recruitment.

Abbreviations: NA = not available; RLS = restless legs syndrome.

Table 6. Design considerations: Is RLS a risk factor for cardiovascular disease and other health conditions/outcomes?

Considerations	Meta-Analysis of Individual Participant Data
Design description	Systematic review of the literature that seeks to determine if RLS is an independent risk factor for cardiovascular disease and other health conditions.
Population	Patients diagnosed with RLS.
Intervention	RLS diagnosis.
Comparator	Matched controls without RLS.
Outcomes	Cardiovascular disease and other health conditions of key interest (depression, motor vehicle accidents, worker productivity).
Timing	Prospective (years).
Setting	Primary care, population studies, out-patient sleep medicine or neurology clinics.
Advantages for producing a valid result	This design is easily done but results will depend on the quality of available studies and the outcomes reported.
Resource use, size, and duration	This design is the most feasible but will require some investigator and analyst investment.
Ethical, legal, and social issues	No ethical, legal or social issues exist.
Availability of data/ability to recruit	Good.

Abbreviation: RLS = restless legs syndrome.

Discussion

This FRN project refined and prioritized research needs relevant to the KQs addressed in the draft CER, "Treatment for Restless Legs Syndrome."[1] We conducted a deliberative process to refine and expand research gaps identified in the CER through conversations with stakeholders with various perspectives of expertise on the topic. This process identified six methodological and 14 topical research questions thought to address identified evidence gaps. We then had stakeholders rank research questions. The highly ranked questions were deemed research needs. Stakeholders prioritized two methodological and five topical research needs.

Addressing methodological research needs will enhance the utility and comparability of future studies of treatments for RLS. A common set of patient-centered and intermediate outcomes, with guidance on interpreting changes in outcomes scale scores, will provide researchers with concrete approaches to collecting outcomes data and determining effectiveness. Guidance on how RLS interventions should be defined in research studies and variables to report in studies as determined by a multidisciplinary panel will, when utilized, enhance the quality of research on the topic.

Advancement in the field needs to address which treatments for RLS are effective for which patients. Additionally, a better understanding of the benefits and harms of treatment for RLS is essential to understanding their effectiveness. Testing specific hypothesis will fill specific evidence gaps identified and prioritized by our stakeholders.

Although one strength of this project is the multidisciplinary perspective brought by broad stakeholder participation, our inability to collect a perspective from a larger sample of stakeholders is also a limitation. The stakeholders participating in this project represented various perspectives on treatments for RLS. However, the prioritized research needs reflect the opinions of these stakeholders and may not be generalizable to the population of stakeholders on this topic.

Conclusions

Addressing research needs identified in this FRN project will help create a broader and stronger evidence base in which clinical decisions can be made. Future research addressing specific research questions is likely to establish a preliminary research agenda on this topic. The highest priority research needs are summarized below:

- What is the sensitivity and specificity of RLS diagnostic tools?
- What are the minimum important differences in RLS outcome measures? Specifically:
  - What IRLS scale scores (or changes in scores) translate to clinically meaningful improvement to assess for treatment effectiveness?
  - Is there a correlation between change in IRLS scale scores and clinically important change in Clinical Global Impression-if so what are those values?
  - What is the correlation of polysomnography outcomes to remission of symptoms?
  - What are the minimum outcomes to be reported?
  - What are the proportions of patients with remission of symptoms (IRLS score = 0), patient reported sleep outcomes, quality of life, etc.?
- What environmental factors are associated with RLS?
  - Is there a geographic/environmental predictor?
- What genetic linkages and biomarkers are associated with, diagnostic of, or causally linked to RLS?
- Is RLS associated with cardiovascular disease and other health conditions-in particular what is the effect of RLS-related chronic sleep deprivation on cardiovascular health?
- What are the short- and long-term comparative effectiveness and harms of treatments for RLS?
- Does tolerance/effectiveness of treatment for RLS vary by demographic/clinical/genetic factors?

References

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Abbreviations

AHRQ	Agency for Healthcare Research and Quality
CER	Comparative Effectiveness Review
EPC	Evidence-based Practice Center
FRN	Future Research Needs
IRLS	International Restless Legs Syndrome Study Group
KQ	Key Question
MCID	Minimum Clinically Important Difference
PICOTS	Population, intervention, comparison, outcome, timing, setting
RCT	Randomized clinical controlled trials
RLS	Restless legs syndrome

Appendix A. Research Gap Questions for Prioritization

Treatments for Restless Leg Syndrome Future Research Questions

Methodological Questions

- What is the sensitivity/specificity of RLS diagnostic tools?
- What is the effect of RLS-related chronic sleep deprivation on cardiovascular health?
- What are the long-term consequences of RLS beyond currently understood sensory problems?
- What is the causal pathway between RLS and insomnia?
- What time frames should be studied to establish treatment benefits and harms?
- Minimum important differences: (a) What IRLS scale score changes translate to clinically meaningful improvement for individual patients? (b) Is there a correlation between change in IRLS and clinically important change in Clinical Global Impression? (c) What is the correlation of polysomnography outcomes to remission of symptoms? (d) What are the minimum outcomes to be reported? (e)What are the proportions of patients with remission of symptoms (IRLS score = 0), patient reported sleep outcomes, quality of life, etc.?

Topical Questions

- What environmental factors are associated with RLS? Is there a geographic/environmental predictor?
- What are the genetic linkages, biomarkers that are associative, diagnostic or causally define RLS?
- Does tolerance/effectiveness of treatment for RLS vary by demographic/clinical/genetic factors?
- What is the short and long term comparative effectiveness and harms of treatments for RLS?
- What is the long term effectiveness/comparative effectiveness of alpha 2 ligands for the treatment of RLS?
- What is the effectiveness of nonpharmacologic therapies for RLS? (mind-body, herbs/natural products, energy fields, and manipulation).
- How might the progression of RLS be delayed?
- Does treatment of RLS improve non-RLS comorbidities?
- Is RLS a risk factor for cardiovascular disease and other health conditions?
- What is the effectiveness of other drugs that are not dopamine agonists or alpha 2 ligands (e.g. opioids and sedative hypnotics).
- Are certain patient characteristics (iron deficiency or disease duration or severity more highly associated with augmentation with dopaminergic therapy?
- Does treatment efficacy differ by RLS symptom severity?
- What is the effectiveness of approved RLS drugs on patient subgroups such as children, older adults, and individuals with secondary RLS?

- How do the findings from published randomized trials apply to patients diagnosed in primary care settings and/or with milder disease of shorter duration?

Appendix B. Search Strategy for Recently Published Studies

Database: Ovid MEDLINE(R) <1946 to July Week 2 2012>
Search Strategy:

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1 "restless leg$ syndrome".mp. (2594)
2 "Ekbom syndrome".mp. (27)
3 Randomized Controlled Trials as Topic/ (81538)
4 randomized controlled trial/ (331851)
5 random allocation/ (75103)
6 double blind method/ (115894)
7 single blind method/ (16375)
8 clinical trial, phase i.pt. (12356)
9 clinical trial, phase ii.pt. (19723)
10 clinical trial, phase iii.pt. (7155)
11 clinical trial, phase iv.pt. (723)
12 controlled clinical trial.pt. (84651)
13 randomized controlled trial.pt. (331851)
14 multicenter study.pt. (146605)
15 clinical trial.pt. (471476)
16 exp Clinical Trials as topic/ (258001)
17 (clinical adj trial$).tw. (171675)
18 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (113479)
19 PLACEBOS/ (31116)
20 placebo$.tw. (137403)
21 randomly allocated.tw. (13776)
22 (allocated adj2 random$).tw. (16099)
23 or/3-22 (1026914)
24 1 or 2 (2607)
25 23 and 24 (401)
26 (case reports or comment or editorial or historical article or letter or news or newspaper article or "review").pt. (4561959)
27 25 not 26 (295)
28 Epidemiologic studies/ (5433)
29 exp case control studies/ (562126)
30 exp cohort studies/ (1191069)
31 case control.tw. (61351)
32 (cohort adj (study or studies)).tw. (61929)
33 (Follow up adj (study or studies)).tw. (33137)
34 (observational adj (study or studies)).tw. (31188)
35 Longitudinal.tw. (110733)
36 Retrospective.tw. (214571)
37 cross sectional.tw. (124581)
38 cross-sectional studies/ (143330)
39 1 or 2 (2607)

40 or/28-38 (1593914)
41 39 and 40 (477)
42 (case reports or comment or editorial or historical article or letter or news or newspaper article or "review").pt. (4561959)
43 41 not 42 (413)
44 27 or 43 (616)

Advanced search for Intervention studies on ClinicalTrials.gov
physical therapy or exercise in the intervention field
and (osteoarthritis and knee) in the condition field

Appendix C. Recently Published Studies

1. Garcia-Borreguero, D., B. Hogl, et al. (2012). "Systematic evaluation of augmentation during treatment with ropinirole in restless legs syndrome (Willis-Ekbom disease): results from a prospective, multicenter study over 66 weeks." Movement Disorders 27(2): 277-83. PMID: 22328464.
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Appendix D. Ongoing Trials

NCT Number	Title	Interventions
NCT00373542	12-week Polysomnography Study of Ropinirole Controlled Release for RLS	Drug: ropinirole CR-RLS
NCT00256854	Converting From Ropinirole IR To Ropinirole Controlled-Release for RLS	Drug: ropinirole controlled-release for RLS
NCT01192503	Safety and Efficacy of Rasagiline in Restless Legs Syndrome	Drug: rasagiline|Drug: placebo (sugar pill)
NCT00806026	Long Term Study Of Pregabalin In Idiopathic Restless Legs Syndrome Patients	Drug: placebo and pregabalin
NCT00314860	Comparing IR Formulation With XR Formulation Of Ropinirole	Drug: ropinirole Extended Release (XR)
NCT01569464	Rotigotine Effect on Functioning and QOL in Subjects With RLS	Drug: Rotigotine
NCT00363857	A Clinical Research Study Testing Ropinirole Treatment for RLS	Drug: Ropinirole
NCT00949806	RLS Treatment With Botulinum Toxin	Drug: BNT (intradermal injection)
NCT00225862	A Clinical Research Study Evaluating Ropinirole Treatment For RLS	Drug: ropinirole
NCT01245777	RLS With Iron Deficiency or Anaemia in the 3rd Trimester of Pregnancy	Drug: ferric carboxymaltose
NCT00367822	Transdermal Lisuride: a Trial for the Treatment of Patients With RLS	Drug: Lisuride; Ropinirole; Placebo
NCT01521663	Safety and Efficacy Study of IPX159 in RLS	Drug: IPX159; Placebo
NCT00247364	A Trial of Levetiracetam and Placebo in the Treatment of RLS	Drug: Levetiracetam (Keppra)
NCT00872248	Neuraxial Anesthesia and RLS in Cesarean	Procedure: Spinal/epidural anesthesia
NCT00355641	Long-Term Safety Of Ropinirole XR In Patients With RLS	Drug: Ropinirole Extended Release (XR)
NCT01494766	Efficacy of Tyrosine in RLS	Dietary Supplement: L-Tyrosine
NCT00479531	Sequential Compression Devices for Treatment of RLS	Device: AirCast Compression Device
NCT00530530	ASP8825 - Study in Patients With RLS	Drug: ASP8825|Drug: Placebo
NCT01562743	A Long-Term Extension Trial From Late Phase II of SPM 962 in Patients With RLS	Drug: SPM 962
NCT00656110	Neuroma Injections to Treat Restless Legs Syndrome - RCT	Drug: Marcaine; lidocaine; Depo-medrol
NCT00584246	Pregabalin (Lyrica) for the Treatment of RLS	Drug: Pregabalin (Lyrica); Placebo
NCT00625547	A Study to Determine the Efficacy and Safety of Cabergoline for the Treatment of Patients With RLS	Drug: cabergoline; levodopa
NCT00239486	Dose Finding Study of Pramipexole (Sifrol) in Patients With Idiopathic RLS	Drug: Pramipexole
NCT00349531	A Phase IV Trial With Pramipexole to Investigate the Effects on RLS Symptoms and Sleep Disturbance in Patients With RLS	Drug: Pramipexole
NCT00197080	Ropinirole XR (Extended Release) In Patients With RLS	Drug: Ropinirole Extended Release (XR)
NCT01537042	A Sleep Laboratory Study to Investigate the Safety and Efficacy of the Rotigotine Skin Patch in Subjects With RLS and End-Stage Renal Disease Requiring Hemodialysis	Drug: Rotigotine; Placebo
NCT00258492	RLS Syndrome Exercise Intervention	Behavioral: Aerobic exercise

NCT Number	Title	Interventions
NCT00136045	Three Different Transdermal Doses of Rotigotine in Subjects With Idiopathic RLS	Drug: Rotigotine
NCT00135993	Four Different Transdermal Doses of Rotigotine in Subjects With Idiopathic RLS	Drug: Rotigotine
NCT00685815	Intravenous Iron Metabolism in RLS	Drug: Ferric Carboxymaltose; Placebo
NCT00200941	Efficacy and Safety Study of Topiramate to Treat RLS	Drug: Topiramate
NCT00199446	Study of Istradefylline (KW-6002) for the Treatment of RLS	Drug: Istradefylline (KW-6002)
NCT00942253	Exercise Training in Dialysis Patients With RLS	Other: Dopamine Agonist and Exercise
NCT01084551	Study of SPM 962 in Patients With RLS	Drug: SPM 962; Placebo of SPM 962
NCT00498108	Phase 3 Open-label Extension Trial With Rotigotine in Idiopathic RLS Subjects	Drug: Rotigotine
NCT00626418	The Effects of Aplindore on the Treatment of Signs and Symptoms of RLS	Drug: Aplindore; Placebo
NCT00263068	An Extension Trial to Investigate Long-Term Treatment With Rotigotine in Idiopathic RLS	Drug: Rotigotine
NCT01495793	Dose Escalating Study of Rotigotine in Pediatric Subjects With RLS	Drug: Rotigotine
NCT00666965	A Placebo-Controlled Study for SPM 962 in RLS Patients	Drug: SPM 962
NCT00243217	Rotigotine RLS Dose Finding Trial	Drug: SPM 936
NCT00627003	A Study to Evaluate the Efficacy and Safety of Cabergoline Compared With Placebo for the Treatment of RLS	Drug: Cabergoline; Placebo
NCT00275236	A Sleep Lab Trial to Investigate the Efficacy and Safety of Transdermal Rotigotine in Subjects With Idiopathic RLS	Drug: Rotigotine
NCT00895232	Iron Sucrose In The Treatment of RLS: The Safety of Three Dose Regimens as Evaluated by Clinical Assessments	Drug: iron sucrose injection (Venofer)
NCT00298623	XP13512 (GSK1838262) Versus Placebo in Patients With RLS	Drug: XP13512 (GSK1838262); Placebo
NCT00991276	Polysomnography Study Of Pregabalin And Pramipexole Versus Placebo In Patients With RLS And Associated Sleep Disturbance	Drug: pregabalin; Placebo; pramipexole
NCT00275457	Efficacy and Safety of Pramipexole in Moderate to Severe Idiopathic RLS Patients	Drug: pramipexole
NCT00144209	Swiss RLS Trial	Drug: pramipexole; levodopa & benserazide
NCT00344994	SWITCH:Restless Legs Patients Switched to Ropinirole From Pramipexole	Drug: pramipexole
NCT01112644	Oxycodone/Naloxone Prolonged Release (OXN PR) Compared with Placebo to Demonstrate Improvement in Symptoms of RLS in Subjects With Moderate to Severe Idiopathic RLS With Daytime Symptoms	Drug: OXN PR; Placebo
NCT00133198	Pramipexole (Mirapex┬«) in Patients With Idiopathic RLS for 12 Weeks	Drug: Pramipexole
NCT01125033	Study of Vitamin C, Vitamin E and Their Combination to Treat RLS in Hemodialysis Patients	Drug: Vitamin C; Vitamin E; Placebo
NCT00152997	Pramipexole (BIoSifrol┬«) Orally Once Daily for 6 Weeks in Patients With Primary RLS	Drug: Pramipexole; Placebo

NCT Number	Title	Interventions
NCT00356096	Phase IV Trial With Pramipexole to Evaluate Safety and Efficacy in Patients With RLS Associated With Mood Disturbances	Drug: pramipexole
NCT00375284	A 6 Week Trial to Study the Efficacy and Safety of a Starting Dose 0.25 mg Pramipexole (Mirapex) in Patients With RLS	Drug: Pramipexole
NCT00152958	A Study in Patients Suffering From Idiopathic RLS Who Responded to a Preceding, 6-month Treatment With Open-label Pramipexole Including Titration	Drug: Pramipexole
NCT01411124	Study to Assess the Effect of Gabepentin Enacarbil on Simulated Driving in Healthy Subjects	Drug: gaba enacarbill; diphenhydramine; placebo
NCT00674310	A Single-Dose, 2-Period, 2-Treatment, 2-Way Crossover Bioequivalency Study of Ropinirole 0.25 mg Tablets Under Fed Conditions	Drug: Ropinirole Hydrochloride
NCT00673088	A Single Dose, 2-Period, 2-Treatment, 2-Way Crossover Bioequivalency Study of Ropinirole 0.25 mg Tablets Under Fasted Conditions	Drug: Ropinirole Hydrochloride
NCT00246051	Comprehensive Police Fatigue Management Program	Behavioral: Sleep Hygiene EducationProcedure: Sleep Disorders Screening and Treatment
NCT00207285	Sleep Disorders Management, Health and Safety in Police	Behavioral: Sleep Hygiene Education Procedure: Screening and Trt of Sleep Disorders
NCT01476124	Drug Drug Interaction Study With Gabapentin Enacarbil and Morphine	Drug: morphine; Placebo
NCT01516372	A Study to Evaluate Effect of Gabapentin on Cardiac Repolarization in Healthy Volunteers	Drug: GEn 1200/6000mg; Placebo; Moxifloxacin
NCT00422994	A Study To Investigate The Effects Of End Stage Renal Disease And Hemodialysis On The Pharmacokinetics Of Ropinirole	Drug: ropinirole dosing for up to 28 days
NCT01455012	Effects of Neupro on Cardiovascular Observations in Patients With RLS	Drug: Rotigotine; Placebo
NCT00419692	RLS Patient Study On Absorption, Distribution, Metabolism And Excretion Of Ropinirole And The Effect Of Food	Drug: Ropinirole