Review Type / Type d'évaluation:	Reviewer 1 / Évaluateur 1
Name of Applicant / Nom du chercheur:	Gilron,Ian
Application No. / Numéro de demande:	362930
Agency / Agence:	CIHR/IRSC
Competition / Concours:	Project Grant/Subvention Projet
Committee / Comité:	Project Grant Competition/Concours de subventions Projet
Title / Titre:	PAin Improvement with Novel Combination Analgesic REgimens: The PAIN-CARE Trial

Concept/Concept

Criterion/Critère: Quality of the Idea/Qualité de l'idée

Rating/Cote: O+

Strengths/Forces: This study will address a potential combination therapy for neuropathic pain which is hypothesised to present less adverse effects while being an effective analgesic. It is creative in evaluating a combination comprising a non-oipioid medication, and this could prove crucial in improving the quality of life of patients.
The goals are clearly defined, clinically pertinent and is supported by the evidence found in the litterature and studies previously conducted by this group. It would be useful in acquiring knowledge, and improving health outcomes for the chronic neuropathic pain population

Weaknesses/Faiblesses: One goal mentioned in the abstract is not found in the design itself:it is stated that the combination of alpha-lipoic-acid and pregabalin will be superior to the combination of 2 sedating agents. No group (figure 1) seems to be receiving such a combination. Has this goal been abandoned in the course of the design of the study ? If not, how will it be evaluated ?

Criterion/Critère: Importance of the Idea/Importance de l'idée

Rating/Cote: O

Strengths/Forces: This is an extremely important study since opioid use for neuropathic pain has increased in recent years, carrying its load of adverse events. These are particularly important to prevent since the population with neuropathic pain tends to be older and thus at risk of having more, and more severe side effects. This population usually presents with many medical comorbidities and may take multiple medications for these, putting them at risk of drug interactions. Finding "safer" and efficacious agents would greatly improve the quality of life of this population

Weaknesses/Faiblesses: The importance of using non-opioid agent in neuropathic pain patients could have been stressed more. In view of the dramatic rise in opioid prescription and 2-4-fold mortality rates increase in prescription opioid users, non-opioid, non-sedative agents are badly needed and their efficacy needs to be carefully evaluated. Furthermore, since there is a hypothesised risk between the observed increase in prescription opioid use and an increase in the prevalence of opioid use disorder, this study would provide alternative treatment options for those at risk of developping this disorder although this goal is outside of the scope the present study

Feasibility/Faisabilité

Criterion/Critère: Approach/Approche

Rating/Cote: O

Strengths/Forces: the double-blind, double-dummy, crossover randomised controlled trial is appropriate and the interventions well described . The main and secondary outcomes measures are adequate as are the tools used.

Weaknesses/Faiblesses: It is mentioned that patients taking other meds (opioids, anti-depressants, NSAIDs, acetaminophen) will be able to continue these at a steady dose, but little is said of how this is going to be evaluated and how their effect will be distinguished. This makes this trial a more pragmatic one, which is clinically relevant but may complicate conclusions
There is no mention of cannabinoids, which are increasingly prescribed in the "pain" population. Additionnally, patients

might use cannabis (and not meet criteria for substance use). Because of its influence on the main outcome, this would need to be tracked.

The study is limited to diabetic neuropathy, which obviously increases internal validity but might limit generalisability. This might be addressed in the limitations, although hardly avoidable at this stage

In addition to "requiring a highly effective contraception" method (how do you inforce that ?), and in order to garantee a significant women participation, it would be advisable to repeat the pregnancy test throughout the study to rapidly identify women who become pregnant. Pregnancy tests are not expensive and would probably not add to the predicted budget

The sample size seems small in view of the fact of potential early drop-outs. Giving drop-out rates from previous similar study would help evaluate the adequacy of the sample size

Since active substance use is an exclusion criteria, how will it be measured (what tool ?) and is tobacco use an exclusion criteria (it usually is not).

Criterion/Critère: Expertise, Experience and Resources/Expertise, expérience et ressources

Rating/Cote: O+

Strengths/Forces: The lead applicant and co-applicants share an extensive expertise in the field of pain research and in the management of large trials

The level of engagement of each of the applicant is described and pertinent

This group has already established a stong institutional support within the Queen's University infrastructure and reports links to primary care facilities.

Weaknesses/Faiblesses: None was identified

Review Type / Type d'évaluation:	Reviewer 2 / Évaluateur 2
Name of Applicant / Nom du chercheur:	Gilron,Ian
Application No. / Numéro de demande:	362930
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Concept/Concept

Criterion/Critère: Quality of the Idea/Qualité de l'idée

Rating/Cote: O++

Strengths/Forces: This research follows in direct line with their previous work. It is a step forward as it aims principally at improving NP control and decreasing side effects, which is the limiting factor to improve NP control. They based their research on their previous research and present compelling arguments in favor of their trial, especially PGB and ALA are proven effective treatment alone and their actions are complementary; contrary to PGB, ALA is not presenting sedative side effects, the major limiting side effect of combined therapy. The aims and goals are well presented.

Weaknesses/Faiblesses: no negative comments

Criterion/Critère: Importance of the Idea/Importance de l'idée

Rating/Cote: O++

Strengths/Forces: The presentation of the importance of the idea is well structured going from comments on prevalence of chronic pain and NP and its health burden; problematic of combined therapy as a common clinical approach; and the additive sedative effect of previous combined therapies. It is therefore addressing a major health care issues too often undertreated. They results will contribute to guide clinicians in the best combination of analgesic drugs.

Weaknesses/Faiblesses: no negative comments

Feasibility/Faisabilité

Criterion/Critère: Approach/Approche

Rating/Cote: O++

Strengths/Forces: The double-blind, double-dummy, randomized controlled, 3 period crossover trial using flexible dose titration, Latin Square crossover design is highly appropriate to answer the question with a feasible study. The dose titration, as planned, is used with reason in view that PGB analgesic effect is dose dependant. They maximize within a pain study any source of bias from other therapeutic interventions. Appropriate outcomes measures. Recruitment is feasible in view in the experience of the center. Adequate statistical analysis.

Weaknesses/Faiblesses: The investigators should address the challenge to insure that subjects may take ALA as it is available without prescription.

Criterion/Critère: Expertise, Experience and Resources/Expertise, expérience et ressources

Rating/Cote: O++

Strengths/Forces: This is a very expert team in RCT in the control of chronic pain and specifically NP and combination therapy.

Weaknesses/Faiblesses: no comments

Review Type / Type d'évaluation:	Reviewer 3 / Évaluateur 3
Name of Applicant / Nom du chercheur:	Gilron,Ian
Application No. / Numéro de demande:	362930
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Concept/Concept

Criterion/Critère: Quality of the Idea/Qualité de l'idée

Rating/Cote: O+

Strengths/Forces: Novel RCT and idea to limit significant AEs of drugs to manage neuropathic pain. High quality methods and strong team. Good track record. Sound rationale for use of both agents.

Weaknesses/Faiblesses: Lack of placebo control but weakness accounted for in application.

Criterion/Critère: Importance of the Idea/Importance de l'idée

Rating/Cote: O++

Strengths/Forces: Neuropathic pain: very few tolerable treatments so important to evaluate new treatments.

Weaknesses/Faiblesses: None evaluated

Feasibility/Faisabilité

Criterion/Critère: Approach/Approche

Rating/Cote: O++

Strengths/Forces: Highly skilled team with significant experience in pain trials. Good methodology to evaluate combination of medications.

Weaknesses/Faiblesses: None evaluated

Criterion/Critère: Expertise, Experience and Resources/Expertise, expérience et ressources

Rating/Cote: O++

Strengths/Forces: Strong multidisciplinary team with excellent track record in trials of this nature.

Weaknesses/Faiblesses: None evaluated

Review Type / Type d'évaluation:	Reviewer 4 / Évaluateur 4
Name of Applicant / Nom du chercheur:	Gilron,Ian
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Concept/Concept

Criterion/Critère: Quality of the Idea/Qualité de l'idée

Rating/Cote: O

Strengths/Forces: Study proposal uses approved drugs (pregabalin, alpha-lipoic acid (ALA)) with the hope of better neuropathic pain control by combination without additive adverse effects – an improvement compared to previous combination regimens (Gilron Pain 2015, NEJM 2005, Lancet 2009).

Mechanisms of action are different (N-type and T-type calcium channel blockade) and presumed to provide synergism. One other trial of similar design (ALA + gabapentin) published (Lopez, 2011) for burning mouth syndrome.

Generic pregabalin will likely become generic after 2019. This trial's result will probably be well received in general practice when done.

Weaknesses/Faiblesses: No phase 2 data to help estimate combined treatment or adverse effects.

Criterion/Critère: Importance of the Idea/Importance de l'idée

Rating/Cote: O

Strengths/Forces: Common chronic and complex pain condition, frequent trial-and-error use of combination therapy (NSAIDs) based on approved drugs that are not likely to receive industry support for testing of combined therapy. Rationale is provided for selected one agent with sedating effect and the other without. Thorough Cochrane Review done (Chaparro 2012).

Weaknesses/Faiblesses: Emphasis on pharmacotherapy, indirectly de-emphasizes lifestyle interventions that might otherwise be important in target population.

Relatively small effect size assumed (mean daily pain 1 point difference on 10 point scale), more statistical difference than clinically meaningful difference (but allows larger sample size).

Feasibility/Faisabilité

Criterion/Critère: Approach/Approche

Rating/Cote: O

Strengths/Forces: 3-period double-blinded balanced cross-over design, efficient but requires rigorous trial mechanism with experienced investigators/coordinators. Relatively small patient numbers, N=54 completers (actual accrued may be larger). Existing pain scales and strict entry criteria. Single-agent arms as internal controls.

Weaknesses/Faiblesses: Main difficulty with 3 cross-over periods will be drop outs…24 weeks total study duration justifiable but fairly significant patient commitment and compliance in addition to disease (symptom) stability. Diabetics only. Success of trial is highly dependent on coordination of research team.

Not sure how many to recruit to account for drop outs.

Review Type / Type d'évaluation:	Reviewer 4 / Évaluateur 4
Name of Applicant / Nom du chercheur:	Gilron,Ian
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Sampling inherently restricted as single centre trial. Would have been more convincing if one or two more Canadian centres have the capacity to participate in the trial.

Criterion/Critère: Expertise, Experience and Resources/Expertise, expérience et ressources

Rating/Cote: O

Strengths/Forces: Excellent track record, previous studies of different drug combinations in same condition.

Independent DSMC in place.

Weaknesses/Faiblesses: Single centre study may limit generalizability.

CIHR IRSC

NOTE

Your application was assessed by the Stage 1 reviewers. Based on the ranking of your application relative to the other applications in the competition, it was identified as highly competitive and did not require further discussion by the Final Assessment Stage committee. As a result, no Scientific Officer notes were generated. The reviewer reports from Stage 1 are available on ResearchNet.

Please refer to the *Notice of Decision* for more information regarding the ranking of your application.

For information regarding the Project Grant Program peer review process, please refer to the *Peer Review Manual - Project* (http://www.cihr-irsc.gc.ca/e/49564.html).

Votre demande a été évaluée par les évaluateurs de l'Étape 1. Compte tenu du classement de votre demande par rapport aux autres demandes dans le concours, celle-ci a été identifiée comme étant très compétitive et ne nécessitant pas de discussion par le comité de l'étape d'évaluation finale. Par conséquent, il n'y a pas de notes de l'agent scientifique. Les rapports d'évaluation de l'Étape 1 sont disponibles sur RechercheNet.

Veuillez consulter l'avis de décision pour plus d'information sur le rang de votre demande.

Pour plus d'information sur le processus d'évaluation par les pairs du Programme de subventions Projet, veuillez consulter le *Guide d'évaluation par les pairs – Projet* (http://www.cihr-irsc.gc.ca/f/49564.html).

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