June/Juin 08, 2011
DCO150GP

Canadian Institutes of Health Research/Instituts de recherche en santé du Canada
Notice of Recommendation/Avis de recommandation

Application Number/Numéro de la demande: 245851
Committee Code/Code du comité: PH1

Applicants/Candidats: Dr. James A. HANLEY

With/Avec: Dr. N. DENDUKURI Z. LIU Prof. E. STRUMPF

Institution paid/ Établissement payé: McGill University

Title/Titre: Methods to measure (and measures of) the (actual) mortality reductions produced by cancer screening.

Primary Inst./Inst. principal: Health Services and Policy Research
Other Related Inst./ Autres inst. connexes: Population and Public Health; Cancer Research

Competition /Concours: Operating Grant
March/Mars 01, 2011

Number in competition/Nbre de demandes dans le concours: 2298

Peer Review Committee Recommendation, for your information and use/ Recommandation du comité d'examen par les pairs, pour fins d'information et d'utilisation:

Committee/Comité:	Public, Community & Population Health
Number reviewed/ Demandes examinées:	41
Application rank within the committee/ Rang de la demande dans le comité:	1
Percent Rank within the committee / Rang en pourcentage au sein du comité:	2.44%
Rated / Cote:	4.71
Recommended Term/ Durée recommandée:	3 years/ans 0 months/mois
Recommended average annual operating amount/ Montant annuel moyen recommandé pour le fonctionnement:	$77,950
Recommended equipment amount/ Montant recommandé pour les appareils:	$0

This document is for information only.
An application rated below 3.50 is ineligible for CIHR funding. For applications rated 3.50 and above, please note that it is the application's rank within the peer review committee that determines whether it is funded, rather than its absolute rating. The final funding decision will be communicated in the Notice of Decision.

Document à titre d'information seulement.
Une demande cotée en dessous de 3,5 n'est pas admissible au financement des IRSC. En ce qui a trait aux demandes cotées 3,50 ou plus, veuillez noter que l'on détermine l'attribution des fonds en fonction du classement obtenu au sein du comité d'examen par les pairs plutôt qu'en fonction du classement absolu. La décision finale relative au financement sera communiquée dans l'Avis de décision.

Review Type/Type dévaluation:	External Referee C/Examinateur externe C
Name of Applicant/Nom du chercheur:	HANLEY, James A.
Application No./Numéro de demande:	245851
Agency/Agence:	CIHR/IRSC
Competition/Concours:	2011-03-01 Operating Grant/Subvention de fonctionnement
Committee/Comité:	Public, Community & Population Health/Santé publique, santé communautaire et santé des populations
Title/Titre:	Methods to measure (and measures of) the (actual) mortality reductions produced by cancer screening.

Assessment/Évaluation:

This excellent proposal develops better methods for identifying gains (reductions in mortality/morbidity) through screening programs. Hanley argues effectively that the simple summary measure which are currently widespread are biased, especially for the scenarios where the effects are not likely immediate. He proposes straightforward methods for a more careful delineation of these effects which require substantially greater information on mortality after screening, data which are currently available but not fully utilized. By partitioning the effects by age and year post screening, Hanley proposes to develop measures of effects over time by age-group and then use these values to produce summary measures of effects. These summaries will be substantially different than those produced by first aggregating the data and will lead to more precise effect statements, principally with less bias, though also with greater precision. His pilot investigations support his theories and approaches.

The implementation of this will require considerable detail at a data level and it will be imperative that Hanley has access to such data. My impression is that the commitments has received in this regard are reassuring enough.

Hanley has had a long record of substantive work in biostatistics and his recent review of the area of screening tests and their benefits puts him in an excellent position to carry out this research. He is supported by a good team of collaborators. I will note that Hanley's major pieces of work tend to be quite substantive; rather than incremental. In these he had addressed important problems and the breakthroughs he has made in advancing thought in biostatistics have been noteworthy.

Review Type/Type dévaluation:	Committee Member 1/Membre de comité 1
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Assessment/Évaluation:

Review of CIHR Grant Application from Hanley et al

Methods to measure mortality reductions from cancer screening

Synopsis

This application proposes to use existing data to develop new methods for estimating the 'real' reduction in mortality that can be expected to result from a cancer screening program. Existing methods significantly under-estimate mortality reductions because of rather crude (and demonstrably inaccurate) methods for estimating them, primarily the lack of accounting for when the deaths occur. Data from several large cancer screening trials and programs will be requested from their PIs for analysis by this group (Hanley et al). If 'raw' data cannot be shared, the investigators will provide computer code which the data stewards can execute, and which will provide statistical information to Hanley et al, which will still allow the proposed analysis to be conducted. This will be done by building on the method already developed by Hanley, and tested & published on ERSPC data (which suggests the real mortality reduction to be more than double that estimated by the original analysis). If the goal is reached (ie a more accurate measurement system is created), the results will be of relevance to all health systems involved in, or contemplating, cancer screening initiatives.

Criterion #1: Research Approach

This application proposes statistical work to develop improved methods for calculating mortality reductions from cancer screening programs, building on recent work by the PI. This novel method is technically intricate, but conceptually logical and straightforward. It is clear from the application, and recent publications by the PI, that the approach is vastly superior to existing methods (which, admittedly, appear disturbingly inadequate), and feasible to implement using real-world data from previously conducted trials and evaluations of screening programs.

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Criterion #2: Originality of the Proposal

Outstanding. The field clearly needs improved methods, and this team is proposing a perfectly suitable and eloquent approach. From the application materials, it appears to be quite feasible for the key ideas to be implemented, and I am very confident that this team can successfully develop new practical measures once they get the data required. This is because of the conceptually straightforward nature of the analysis – which is no insult to the work, as the simple fact is nobody has done it yet (likely due to the novel thinking, and intricate work required to actually carry it out).

Criterion #3: Applicant(s)

Outstanding: the PI has clearly and persuasively demonstrated both the inadequacies of existing methods, and the feasibility of key aspects of the new approach using existing data. He has a long and distinguished history of involvement in cancer screening research, and has connected with key investigators leading the major studies whose data will be used in this project (letters of 'support in principle' are included for several, though not all). The co-applicants will be able to provide additional supports as needed. A new PhD student, already working in this area, will also contribute significantly (and it's nice to see her listed as a Co-Applicant, not just a Trainee).

Criterion #4: Environment for the Research

Excellent: As largely a data analysis project, this study could be carried out in any of a number of places, and the McGill environment is likely as good as any. More importantly, the PI's experience and reputation in the field and network of contacts will be key to finalizing access to the data required to conduct this study.

Criterion #5: Impact of the Research

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Assessment/Évaluation:

The potential impact of this project is stunning. If it can be accurately demonstrated that the mortality reductions associated with cancer screening are indeed as large as the results of the PI's preliminary 're-analyses' suggest, then large benefits may be reaped by populations worldwide - wherever effective programs are implemented. As (astutely) stated in the application, this project will answer the critical 'real-world' questions that policy makers and the public need answered – rather than just the statistical questions that researchers and trialists usually ask.

Issues / notes:

- This is a remarkably strong and exciting proposal. Granted, part of what makes it so appealing is the appalling inadequacy of existing methods. But regardless, what we want for every program is accurate assessments of the potential risks and benefits. This project, if successful, will radically improve our ability to measure mortality reductions – the ultimate benefit/outcome (and reality for patients).

Potential concerns

- Uncertainty of data availability: this project ultimately depends on data not currently held by the investigators. That said, they have very positive 'support in principle' letters from several key data holders, and have very recently thought of a work-around for data providers who are unwilling or unable to provide 'raw' data to this group. Presumably, they will be successful in gaining access to the required data based on their long-standing relationships, and preliminary conversations.

- Timing – despite the support letters, I am somewhat concerned about the timing of actual delivery of the data to the researchers. These kinds of approvals can take months to get 'signed', and additional months for the data to be delivered in the required form. Hopefully, things will work as planned, and if delays in data delivery are experienced, perhaps an extension of research funds could be arranged?

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- Costs – the budget contains only $15,000 to reimburse data providers for their work to prepare and provide data. This seems like a modest budget, and I would feel better if I saw evidence that the data providers agree that this sum is adequate. Presumably, this was considered by the applicants, otherwise a different amount would have been requested – but it wasn't directly addressed or justified in detail, so remains a concern.

- Ethics – presumably, all the data being requested by this group were collected by the original study investigators with consent (research studies) or implied permission ('service' screening programs) to use the data for primary and secondary research purposes which would cover the data use proposed here. If not, the study cannot proceed - but presumably the applicants considered this, and just didn't note it in the application.

Budget & timeline:

- Timeline: 3 years seems reasonable, pending actual delivery of data.

- Budget: Main items and staff seem reasonable, though the PhD student may have to settle for the standard CIHR stipend to maintain fairness and transparency. Also, as stated above, data provision costs do not appear to have been precisely quoted from the providers, so may exceed the $15,000 requested. If there is a small shortfall, this may be resolvable by re-allocating funds from other aspects of the study, but if there is a larger amount, additional funds may be required.

Review Type/Type dévaluation:	Committee Member 2/Membre de comité 2
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Competition/Concours:	2011-03-01 Operating Grant/Subvention de fonctionnement
Committee/Comité:	Public, Community & Population Health/Santé publique, santé communautaire et santé des populations
Title/Titre:	Methods to measure (and measures of) the (actual) mortality reductions produced by cancer screening.

Assessment/Évaluation:

Introduction

This grant seeks to impact how data from cancer screening RCTs and programs are analyzed to produce more accurate results that are better able to answer important policy questions. Their method takes into account the expected zero-reductions in mortality early on in a screening program and later on after the screening program has finished. By accounting for the time-specificity of screening, the timeline of impact and the dynamic nature of impacts of screening, their proposed process corrects the current method that systematically underestimates the mortality reductions produced by screening. The grant seeks to create a model that would use three core parameters to project the effect achievable in the future if a specific regimen of screening was started today or the effect of screening started previously (instead of the current research focus of significant or not based on the p-value). In addition, this new method will improve the design and analysis of further screening trials.

The method purposed in the grant claims to improve upon the current standard method (He & Zelen approach) by making sample size calculations easier as well as "…the time-specificity and parameters are used in and extracted directly from the analysis."

The authors do state clear plans to test various aspects of the model to ensure its appropriateness. This includes testing the feasibility, accuracy and performance of their approaches in addition to the implications of varying follow-up time or the numbers and/or timing of deaths in relation to the timing of screening.

Strengths

· This grant was well-written with coherent arguments that were supported methodologically as well as by current literature. There were clear and logical arguments that highlighted the enormous potential impact of this initiative. The authors address how their new measure would support policy decisions resulting in clear outcomes from their initiative.

· The investigators propose to develop a method that allows them to get information from past trials without needing the raw data helping to facilitate data sharing of sensitive information.

· Their method would enable estimates on how many cancer deaths were prevented each year as a result of the cancer screening (what policy makers want to know)

· Improve upon current reporting methods, which underestimate the effect of screening by averaging overall deaths prevented over the entire time period of analysis (includes (expected) zero-reductions early on and later on). Their method analyzes data using time-specificity!

o Makes sense logically (i.e. time lag in screening benefit)

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· Using time-specific mortality rate ratios unbiasedly measures the timing and magnitude of the reductions from different screening regimens AND isn't biased by length of follow-up time
o Show that "… the shorter and more inadequate the follow-up, the more heavily is the overall % reduction over this period (incorrectly) weighted towards the lesser reductions in these early follow-up years."

· Their claim is that statistical method will make sample size calculations easier.

· The propose to create a method so can get information about the parameters without needed the investigators from other studies to give their raw data

· Model being created so can handle data from a single screening trial with same screening regiment, different screening frequencies and multiple screening trials with numerous differences in designs (p. 9)

o Going to test the feasibility, accuracy and performance of their approaches (using stimulated data though) in addition the implications of varying follow-up time as well as the numbers and timing of deaths in relation to the timing of screening

· Going to establish guidelines for data needed to estimate the 3 parameters and steady-state mortality reduction for future trials AND going to apply this method to past trials

· Team: biostatisticians and a health economist with lots of experience in the area (as well as support from some of the trials' authors whose data is going to be needed)

Weakness

Unfortunately, it was unclear if the function they propose to develop is sufficient to make judgments on the trial or if it results in too much data reduction.
The authors have done a review that found numerous examples of underestimation in cancer screening RCTs but I was unsure that this claim that this is **always** the case.
The model is being created so it can handle data from a single screening trial with the same screening regimen and a single trial with different screening frequencies in addition to multiple screening trials with numerous differences in designs. I am unsure if the authors may not be properly accounting for the heterogeneity between different trials or screening regiments.
The authors claim that this method would apply to RCTs and population screening data, but this is unclear as

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most of the application focuses solely on RCTs.
There is a need for an evaluation plan that tests the utility of this new measure as well as measures the outcomes to ensure that this approach really does result in innovations within the field.
Not sure there is evidence of the accuracy of their new estimates of the ERSPC data (even if yes, how do you know it will work with the other trials? How do you know the early and/or late reduction windows are not affected by factor(s) not considered?)

Summary

If their method works and is accurate, it would have significant impacts on screening trials and programs as well as help bridge gap between research and policy and more uniform public message

Review Type/Type dévaluation:	SO Notes /Notes de l'agent scientifique
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Assessment/Évaluation:

The committee was very enthusiastic about the project.

Strengths of the application included originality of the project, methods have the potential for high impact, well-written grant, good team, and smart work-arounds for data access.

Budget as requested.