

Adapted from notes generously provided by Dr. William Colmers
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What does an internal reviewer need to evaluate your proposal fairly?

1) Your assumption should be that the reviewer is NOT an expert in the field (i.e., they are NOT familiar with jargon, or the ins and outs of many of the techniques, their limits, etc.)

Please take time to explain the basics briefly but cogently, and explain to me clearly why what you're doing is important to the field.

EXAMPLE:

Neuroscience covers everything from behavior to molecular biology. I'm in the middle as an electrophysiologist. Place your work in a larger context briefly but clearly. If you make the effort to include the reviewer in the beginning, the reviewer will gamely try to follow the rest.

2) A clear statement of what you are trying to achieve in the application

Please don't make reviewers try and dig out what you really meant. Linguistic scholarship is a field I'm saving for my next career. Write efficiently.

EXAMPLE:

The literature in any field is enormous. Pick the few references that will help the reviewer evaluate the state of the field and where your work fits in. State clearly what the hypotheses are and how you arrived at them.

3) A clear outline of the studies/experiments. This is after all what you are ultimately judged by.

Make certain before you submit a grant that the experimental/scientific logic is clear. If there are problems and concerns with the interpretation, let the reviewer know how you will solve/resolve it. Run it by a colleague in the field who does something different than you do.

EXAMPLE

Write the experimental section clearly, so the reviewer knows that you are isolating a protein made by cells in culture that are stressed by having been hit with a hammer (HSP). Let the reviewer know in simple terms how you know that the HSP you isolate is from these cells, and why your model of dropping a brick on the cultures mimics the natural problem.

4) A GOOD SUMMARY PAGE. Reviewers are going to read this first because they need to get a sense of the application, and they are likely reading 8 other grants...on a plane... late at night...in economy class!

Try to summarize the relevance to the field in one introductory paragraph of reasonable length. The next should emphasize your contributions to the field and the remainder should have the objectives

of the grant in logical order. If appropriate, (and it usually is) state things in terms of the hypotheses to be tested. Repeat these in the grant, but not word-for-word. Also, DO NOT repeat the entire summary page as the first page of the proposal. This is bad technique and appears intellectually lazy – a very bad signal to the reviewer!

EXAMPLE (experimental science)

Toejam is an important body product. Alterations in toejam expression have been linked to mopery, dopery and popery, and therefore have important implications for public health; inappropriate toejam expression causes millions of dollars and untold suffering in Canada.

My laboratory has isolated a human gene linked to the inappropriate expression of toejam in a community of frogcatching Huguenots in central Manitoba. Linkage analysis suggests that this gene is on chromosome 17, near the *aab*, *xyz*, and *ragR1* sites. We have recently isolated a candidate gene from cultured human fibroblasts from members (carriers and noncarriers) of this community, using differential display methods. We propose to characterize this gene (*tj1*) and determine whether it is responsible for human toejam expression, by testing the following hypotheses:

1) *The tj1 gene product is responsible for regulation of toejam expression.* We have developed a human toe cell culture system in which toejam expression can be induced by phorbol ester application. We will test this hypothesis by using stably transfected human toe cells...

2) *The human toejam gene (tj1) linked to CFTR expression.* Evidence suggests that CFTR carriers suffer from inappropriate toejam expression. We will test this hypothesis by..

3) *Expression of tj1 is regulated by CREB elements and AP1 sites in the promoter region.* Evidence from homologous recombination in mice suggests that the possibly related murine gene (*mj1*) is regulated by both AP1 and CREB sites in the upstream promoter region. We propose to test this hypothesis by...

The results of the experiments will increase our understanding of how human toejam expression is regulated, and should lead to methods of clinical detection of inappropriate toejam expression.

EXAMPLE (clinical science)

Toejam is a common clinical finding, which has been linked to increased morbidity and mortality, especially in the elderly and patients with diabetes mellitus. Its detection and control has important implications for public health; inappropriate toejam build-up costs millions of dollars annually and negatively impacts the quality of life of many Canadians.

Our research program has studied the toejam issue in a variety of clinical settings including the emergency department, primary care and community groups in central Manitoba. Data linkage suggests that this disease is more common than previously recognized and further work is urgently required on the prevention and treatment of the complications. We have recently identified an effective and innovative treatment called HAST (**H**ydro-therapy of **A**symptomatic and **S**ymptomatic and **T**oejam) and collaborators in Germany (HAST-plus) and Australia (HAST-2) have demonstrated the effectiveness of treatment modifications. We propose to further explore the treatment of toejam using HAST and its derivatives to determine the effectiveness of this treatment, by testing the following hypotheses:

1) *The epidemiology of symptomatic toejam is poorly understood.* We plan to prospectively identify and follow consecutive patients seen in 10 primary care settings in Alberta to identify patients with toejam accumulation as well as toejam associated illness (TAI) using the reliable and validated Toejam-tool (TT).

2) *HAST is an effective form of therapy for symptomatic patients.* Evidence suggests that patients with TAI benefit from antibiotics; however, pilot evidence from our research program suggests that irradiation of toejam enhances TAI recovery and prevents relapses. We will test this hypothesis using a large, multi-centered randomized controlled trial of TAI patients identified from the surveillance project above.

3) *Factors associated with response.* Not all patients with toejam respond to HAST and the factors (e.g., age, sex, SES, previous infection, co-morbidities, etc.) associated with treatment failures are poorly understood. We propose to resolve this knowledge gap by conducting logistic regression analyses on those receiving treatment to identify clinically and statistically important factors associated with treatment response.

The results of these studies will increase our understanding of human toejam epidemiology and management, and should contribute to clinical practice guidelines designed to standardize the care provided to this important group of patients.

Long-term Outcomes and Health Care Utilization of Patients with Toejam: Extended Follow-up of a Prospective Population Based Cohort

Background: The annual incidence of Toejam is 12/1,000, and in Canada it accounts for 60,000 emergency department (ED) visits, 640,000 days of restricted activity, and 5,000 toe amputations yearly. Toejam outcomes are potentially affected by numerous factors (SES, co-morbidities, age, sex, etc.), but current evidence is based on small (<500 patients) short-term studies. Moreover, treatment options are limited. One small randomized controlled trial (n=250) has suggested that Hydro-Therapy of Asymptomatic and Symptomatic Toejam (HAST) therapy can substantially reduce the risk of hospitalization in toejam patients. In Alberta, it is estimated that 70% of all toejam patients presenting to the ED receive HAST therapy. Despite the frequent occurrence of toejam, there is currently limited data available to clinicians regarding the natural history of toejam and long-term outcomes associated with HAST therapy.

Objective: Using multiple administrative databases linked to an established population-based clinical registry, our objective is to investigate and understand the long-term (up to 5 years) sequelae of an episode of toejam in patients initially treated in the ED and the potential impact of HAST therapy in reducing the risk of hospitalizations, toe infections, and amputations in patients with toejam.

Specific Aims: To determine in patients admitted to the ED with an episode of toejam: (1) rates and clinical correlates of long-term hospitalization, toe infections, and amputation; (2) impact of SES, functional status, comorbidities, and age on recovery and long-term healthcare use, and (3) clinical outcomes associated with the use of HAST therapy.

Preliminary work: Between 2005 and 2006, as part of a clinical pathway for managing toejam in Alberta, we prospectively created a population-based cohort of all adult outpatients with toejam seen at any of the emergency departments in Edmonton or Calgary. Almost 9000 patients were included, and clinical (e.g., Toejam Severity Index, pre-existing comorbidities), functional status (30% with impairment), and use of HAST therapy at time of discharge (62% sent home with HAST therapy) was collected. Pilot data suggests high rates of morbidity (>13,000 toejam related hospitalizations and 600 toe amputations over 5 years of follow-up). In unadjusted analyses, pre-morbid functional status and diabetes are strongly (OR>2-3) and significantly ($p<0.01$) associated with long-term adverse events. Despite widespread prescribing, no clinically important effect on hospitalizations or toe amputations was observed with HAST therapy (OR 0.95, $p>0.05$); however, fully linked data is required for multivariate analyses. To our knowledge, this is the largest and longest followed (5 years) cohort of toejam patients that will have ever been assembled and evaluated.

Research Plan: We will complete and finalize linkages to our established population-based and clinically-rich cohort of ~9000 adults with toejam to multiple high-quality and previously validated administrative databases to ascertain the following outcomes: (1) mortality (Vital Statistics), (2) emergent visits and hospitalizations (AB Health), (3) physician visits (AB Health), and (4) medications for those 65 years and older (Blue Cross). Once this dataset has been assembled, we will use descriptive statistics to calculate incidence rates and characterize the population. Then, using survival analysis and proportional hazards framework, we will explore the independent associations between baseline clinical information and long-term outcomes such as all-cause or toejam-related hospitalization, infections, and toe amputations. Using multivariate proportional hazards or logistic regression models as appropriate, we will determine if outcomes differ according to routinely collected clinical data, as well as specifically examine the impact HAST therapy compared to those not receiving HAST therapy on our longer-term outcomes.

Significance: Rates of toejam are rising in North America despite optimal treatment. Our results will permit better risk stratification and better discharge care plans for patients with toejam. HAST is a new and understudied treatment option for toejam patients; however, the true impact of this therapy is unclear and large-scale randomized trial evidence will not be available to address these issues in the near future. We feel that our proposed study will provide important insight into the relative effectiveness of HAST therapy. Our proposed study *will be the first* to evaluate the effectiveness of HAST in real-world patients and will help clinicians, decision-makers, and patients weigh the risks and benefits of HAST therapy.

Understanding and Intervening on Risk Behaviours for the Toejam Epidemic in Canada

Background: Toejam prevalence has tripled in Canada over the past decade, with the greatest increases among seniors, university students, and among northern populations. Toejam build-up has been linked to increased morbidity and mortality, costs millions of dollars in health care expenditures annually and negatively impacts the quality of life of many Canadians. Early clinical studies suggest Toejam is resistant to treatment. The need for prevention is clear. A growing body of evidence links Toejam with high risk behaviours, primarily prolonged wearing of wool-lined footwear. Early social marketing campaigns to address risk behaviours have been largely ineffective in motivating behaviour change. The need to understand the social and environmental context of footwear use is an important first step in creating effective interventions to change behaviour as a determinant of Toejam incidence.

Research Questions: From the perspectives of frequent wool-lined footwear users at high risk for Toejam, 1) **what factors influence their footwear preferences and wearing behaviours?** and 2) **what factors may decrease barriers to footwear behaviour change for Toejam risk reduction ?**

Preliminary work: Our research group conducted pilot focus groups with university students in a northern Canadian city (Edmonton) and revealed that wool-lined boot use was considered fashionable, trendy and attractive to the opposite sex. These positive perceptions influenced the purchase of very expensive and extensively marketed wool-lined boots originating in Australia. In individual interviews, most students admitted to purchasing and wearing inexpensive imitations. As students indicated the boot lining was comfortably fuzzy, few reported risk reduction strategies such as the use of socks. We have yet to explore perceptions of seniors who have been documented as wearing wool-lined slippers for extensive time periods.

Research Plan: High Risk Population 1: University Students. Building on our preliminary qualitative work with university students, we propose to repeat focus groups with students in 2 other universities in more southern or warmer locales (Vancouver, Calgary). Focus groups will follow a guide similar to that used in Edmonton. The goal is to elicit more varied perspectives on wool-lined footwear use. Following completion of all focus groups, we will develop, validate and administer an electronic questionnaire to a random sample of 10,000 university students across Canada to assess: 1) prevalence and duration of wool-lined footwear wearing behavior by geographic and demographic characteristics, 2) attitudes toward wearing wool-lined footwear, 3) exposure to marketing of wool-lined footwear, 4) wool-lined footwear purchasing patterns, 5) barriers to changing footwear use patterns (including risk reduction behaviours), 6) perceived factors enabling behaviour change. If additional determinants of wool-lined footwear use are identified in subsequent focus groups, the questionnaire development will incorporate the broader perspective.

High Risk Population 2: Seniors. We will conduct focus groups with seniors living in 3 seniors' complexes (Private, public, and subsidized) in each of the following cities: Edmonton, Calgary and Vancouver. Focus groups will explore seniors' perceptions of wool-lined footwear use, including comfort, warmth, expense, social acceptability, and any other perceptions that seniors may offer. Following the same rationale as with the students, we will then develop, validate and administer (in person) paper and pencil questionnaires at seniors' gatherings in each of the three cities to capture a broader range of perspectives.

Significance: Our proposed study *will be the first* to explore social and environmental determinants of Toejam from a risk behaviour perspective. Our results will inform interventions to promote lower-risk footwear use among populations known to be at high risk for Toejam. As prevention is key to managing the Toejam epidemic, exploring means of preventing risk behaviours is a first and essential step.

Please take the time to fill out this short survey regarding resources found on this webpage. This survey will take approximately 1 minute to fill out. To fill out the survey, please go to the following link:

[University-wide CIHR Special Project Questionnaire about Resources](#)