TITLE PAGE

The title of the article: Does research pay? Estimating the payoffs from cardiovascular disease research in Canada

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Running Head: Estimating returns on research investment

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Abstract (222 words)

Background: Investments in medical research can result in health improvements, reduction in health expenditures, and secondary economic benefits. These "returns" have not been quantified in Canada. Our objective was to estimate the return on public/charitable-funded cardiovascular disease (CVD) research in Canada,

Methods: The primary outcome was the internal rate of return (IRR) on public/charitable-funded CVD research. The IRR is the annual monetary benefit to the economy for each dollar invested in CVD. Calculation of the IRR involved four steps: i) measuring expenditures on CVD research; ii) estimating the health gains accrued from new CVD treatments; iii) determining the proportion of health gains attributable to CVD research and the time lag between research expenditures and health gains; and iv) estimating the spillovers from public/charitable sector investments to other sectors of the economy.

Results: Public sector research expenditures on CVD from 1981 to 1992 were $392 million ($2005); health gains associated with new treatments from 1994 to 2005, time lag 13 years) were 2,213,776 quality-adjusted life-years. We calculated an IRR of 20.6% for CVD research funded by the public/charitable sector. Thus, every $1 invested in CVD research in the public/charitable sector will yield a stream of benefits of roughly $0.21 to the Canadian economy per year, in perpetuity.

Interpretation: Canadians obtain relatively high health and economic gains for every dollar spent on CVD research.

Key words: cardiovascular medicine, health economics

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death and reason for hospital admissions in Canada (1). For every $69 spent on cardiovascular care in Canada, $1 was spent on research (2, 3). Increasingly frugal governments want to ensure that public funds are spent in the most effective way. Decisions to allocate funds to medical and health research must meet the same standards as other public investment decisions, those of effectiveness and cost effectiveness (4). Failure to meet these standards may lead funders to direct their resources to areas that demonstrate greater impact on the economy and society. One way to ascertain the overall impact of research is to determine its return on investment. The internal rate of return (IRR) is often used to measure and compare the attractiveness of investment. In this context, it can be estimated by comparing the cost of research investments to the monetary value of research-related health gains, in addition to other economic benefits. To date, no study has examined the relationship between Canadian research spending and improvement in health outcomes. We address this gap in knowledge by comparing the benefits accrued from public/charitable-funded CVD research in Canada with its cost to obtain an estimate of the IRR.

METHODS

We estimated the IRR on CVD research, utilizing a previous published approach (5).We used a "bottom-up" payback approach, which involves estimating research costs and health gains over a given time interval (6). In contrast to econometric top-down methods,

our approach examines economic and research-related health gains in greater detail, with a closer linking of health research outputs to specific research projects.

We calculated several items to determine the IRR from CVD research:

a) research expenditures on CVD from the public/charitable sector from 1975 to 2005
b) health gains and costs associated with new CVD treatments and procedures
c) the link between CVD research and health gains
d) spillovers from public/charitable sector investments

We discuss each of these components in detail in the subsequent sections.

Public and Private Sector Research expenditures on CVD

We compiled a list of the major granting agencies in Canada (Table 1) in order to estimate public/charitable research expenditures. Next, we found additional organizations through a comprehensive internet search of links on the websites of organizations that had been identified and entering keywords, such as "health" and "research", into search engines. Finally, we made use of the Reference Lists of health research in Canada (which include data collected by the former Medical Research Council of Canada) to provide us with additional funding organizations that were not captured in our search, either because they no longer exist or changed their name over the years. Once our list was complete, we contacted each organization to obtain CVD-related expenditures from 1975 to 2005. Information was provided directly by the organization, or obtained from its annual reports or the reference lists. We reviewed all grants and fellowship/scholarship titles

(and summary/key words, when available) to determine its inclusion (i.e., related to heart and/or peripheral vascular diseases) (7). We also estimated past research expenditures of the private sector (pharmaceutical and non-pharmaceutical industries) using data from the Patented Medicine Prices Review Board (8) and Statistics Canada (9). Unfortunately data for this sector were not available for all years of our analysis. Data were also not available by therapeutic area; therefore, we assumed that 15% of all private sector expenditures were spent on cardiovascular research based on previous work (5, 10). For each funding sector, we estimated the value of expenditures in 2005 Canadian dollars using Statistics Canada's Consumer Price Index (CPI). Figure 1 depicts expenditure trends for CVD research for each sector and for the years of available data.

Health gains and costs associated with new CVD treatments

We estimated the magnitude of health gains and costs associated with new CVD treatments between 1994 and 2005, using an adaptation of the Ontario IMPACT model (7), a validated epidemiologic model of CVD. This required: 1) estimating the number of unique users for each cardiovascular treatment; 2) determining the magnitude of health gains for each new treatment, expressed in quality-adjusted life-years (QALYs); and 3) assigning a monetary value to health gains. We modified the IMPACT model to obtain estimates on the number of unique users for different interventions to treat/prevent CVD for all of Canada (7). We examined nine mutually exclusive treatments and 47 medical and surgical therapies (Table 2). To obtain estimates of the QALYs gained for each intervention and the corresponding marginal lifetime costs, we performed a systematic review of the literature (11-52). Whenever possible, we used Canadian studies to obtain

QALY and cost estimates. We converted costs to Canadian dollars, when Canadian studies were unavailable, using the Purchasing Power Parity value (53). All costs were inflated to 2005 Canadian dollars using the CPI. We converted QALY gains into monetary values by multiplying them by $50,000, an assumed monetary value of a QALY (5). We then calculated the net monetary benefit for each CVD intervention by subtracting the net health care costs from the monetized QALY gains.

Link between Canadian CVD research and health gains

The next steps involved estimating the "link" between expenditures and health gains. Several unresolved methodological issues when evaluating the IRR were addressed in this step (54): 1) whether to attribute all health gains realised to medical research or to attribute some to other types of research or non-medical factors, such as income or housing conditions, and knowledge translation and exchange activities (attribution issue); 2) how to determine the proportion of these gains that were due to Canadian research (Canadian contribution); and 3) how to determine how long it took for research expenditures to "translate" into health gains (time lag). To determine the attribution factor, we reviewed the social determinants of health literature, which suggested that 32% to 56% of the variation in Canadians' health outcomes is explained by socioeconomic factors (55) (i.e., 44% to 68% is due medical research). Furthermore, Bunker (56) created inventories of established life-extending outcomes due to preventative or curative care for individual conditions and estimated that half of the 7.5 years of increased life expectancy since the 1950s can be attributed to medical care. Thus, we estimated that roughly 70% of health gains in CVD interventions were attributable to medical research.

To estimate the proportion of global health gains attributable to Canadian CVD research, we employed two distinct approaches: a bibliometric search and the analysis of patent data (57). For the first approach, we categorised search results by country of primary author; for the second one, we examined the number of patents by country of ownership. Our bibliometric estimation method indicated that Canada's average contribution to global health gains was roughly 5% (Figure 2), while the patent data method showed that Canada owns close to 7% of total patents in the field (Figure 3) (57). Combining both results, we determined the overall Canadian contribution to global CVD research to be approximately 6%.

To determine an appropriate time lag factor, we reviewed the literature to assess previous approaches (5, 58, 59). We drew upon 11 robust papers from the Contopoulos-Ioannidis et al. study (59) and determined our average time lag to be 12.8 years with a standard deviation of 4 years. We also considered the case in which time lag followed a normal distribution. Thus, an estimated time lag of 12.8 years implied that for health gains achieved during 1994-2005 (the time horizon of our model), we were interested in expenditures during 1982-1993.

Spillovers

Beyond health gains, medical research can produce economic gains in the form of additional national income (social return). Based on previous work and the existing literature (5), we employed two approaches to quantify spillovers obtained from

public/charitable research. In the first approach, we estimated the gains obtained from private research and development (R&D) stimulated by public/charitable research, and then the social rate of return to private R&D stimulated by public/charitable R&D. In the second approach, we estimated directly the social rate of return on public/charitable research generated by all transmission mechanisms (5). Combining both methods, the more conservative of the two suggested a social rate of return of 31%.

Internal Rate of Return

The IRR can be described as an "annualized effective compounded rate of return". An investment is considered acceptable if the IRR is greater than an established minimum rate of return. Most private sector firms use a minimum rate of 12%, based on typical returns of the S&P 500, a stock prices index of the 500 largest companies in leading industries of the US economy.

Sensitivity Analyses:

We varied the values of all input parameters to understand how our IRR differed under different scenarios:

a) Optimistic scenario: time lag of 10 years; Canadian contribution factor of 8%; medical research contribution of 100%; QALY value of $60,000.
b) Pessimistic scenario: time lag of 17 years; Canadian contribution factor of 4%; medical research contribution of 50%; QALY value of $40,000; higher value of public/charitable research expenditure (25% higher) to allow for uncertainty in estimating this parameter.

See the Appendix for additional details.

RESULTS

Research expenditures on CVD

We found that in 1975 public/charitable expenditures were roughly $13 million, rising to $41 million in 1990 and to $96 million in 2005. Private sector pharmaceutical research expenditures were about $36 million in 1988, rising to $177 million in 2005; private sector non-pharmaceutical research expenditures were about $17 million in 1994 and approximately $60 million in 2005. In total, Canada spent approximately $333 million on CVD research in 2005.

Health gains and costs associated with new CVD treatments

Table 2 summarises our results. Statins and aspirin represented the groups with the most unique users during our analysis period. Heart transplant and primary CABG were the CVD interventions with the fewest unique users. We found that cardiovascular treatments were responsible for a gain of 2.2 million QALYs between 1994 and 2005. The largest QALY gains were associated with non-starting smoking and hypertension treatment. The categories with lowest QALY gains were spironolactone and warfarin therapy. The monetary value of all of the QALY gains was approximately $111 million. For all categories/treatments, we obtained total costs of roughly $20 million. Lifetime net costs (cost of treatment minus costs averted by treatment) per user ranged from 0 (aspirin) to $68,287 (heart transplant). In total, we obtained a net monetary benefit of treatment of

$91 million. ACE inhibitors used to treat chronic angina and CHD and aspirin yielded the highest net health benefits. The most expensive items, such as heart transplant and CABG surgery, were among the interventions with the smallest net health gains. Angioplasty was the only intervention that exhibited a negative net health gain.

Internal Rate of Return

Our aggregated results on the economic returns to research expenditures are in Table 3. Our baseline scenario included a time lag of 13 years, a Canadian contribution to global research of 6%, a medical research contribution to health gains of 70%, and a QALY value of $50,000. These parameters led to an IRR of 20.6% (for both point estimates and distribution-based estimates of time lag). This value increased to 35.1% under our optimistic scenario and decreased to 10.3% under our pessimistic scenario. When we incorporated private sector research expenditures into our analysis, we found that our IRR was 12.9%; with a spillover rate of 31%, our social rate of return was 43.9%.

INTERPRETATION

We found an IRR of 20.6% for investing in CVD research by the Canadian public/charitable sector. Thus, for every $1 spent on public/charitable CVD-related research, Canadians will receive an income stream of about $0.21 per year in perpetuity. Considering a minimum acceptable rate of return of 12%, this investment is quite attractive.

This analysis was commissioned by the Canadian Institutes of Health Research to understand how much "bang" we were getting from our research "buck", and whether investing in CVD research is worthwhile from a population health perspective. Governments and policy makers are often confronted with how best to allocate scarce resources among competing priorities; as such, choices regarding research fund allocation must be based on effectiveness and budget impact. A pertinent question is how Canadian medical research funds should be allocated, in particular regarding CVD research. Evidence from a decade ago suggests that the economic impact of CVD on the Canadian health care system can be substantial — $18 billion in direct and indirect costs per year (60). Thus, the need for continued monitoring of CVD investment and treatment outcomes remains. Furthermore, our IRR of 21% is an excellent rate of return. Should we divert research funds from other areas? We cannot answer this question directly as we are not aware of studies that have estimated the IRR for investing in research for other diseases; nonetheless, our analysis suggests that investing in CVD research is worthwhile. In tandem, funds should be devoted to research that focuses on CVD-related risk factors, such as obesity and diabetes, to avoid reversing the recent declines in CVD-related mortality (1).

Contributions

Our work represents several contributions to the field. It provides a comprehensive time series of CVD research expenditures. It suggests an estimate of an attribution factor based on the social determinants of health literature, an estimate of Canada's contribution to global medical research and an estimate of the social rate of return on public/charitable

medical research for Canada. Methodologically, our analysis offers a novel approach to estimate the attribution factor by modelling time lag as a distribution. It also proposes improved methods to estimate the number of users in each patient group/intervention and the differential treatment of health gains for smoking quitters and non-starters. Finally, this analysis is the first to estimate the IRR of investing in CVD research in Canada.

Our IRR estimate differs from the one estimated for the UK, suggesting that Canada has received a greater return for its investment in CVD research. This is mainly due to differences in data sources, Canada's relatively low research expenditures and the underlying assumptions in our analysis. Alternatively, it may indicate that Canadians are "free riders", disproportionately benefiting from research conducted abroad. Other studies also suggest that Canadian returns on research are larger. Buxton et al. (5) applied their methodology to mental health research in the UK and found an IRR of 7%. Another study that examined research investments in the U.S. agricultural field found an IRR of 17% and a social internal rate of return of 29% (61). While our results suggest that Canada obtains higher returns on research, this finding could in part be explained by the assumptions employed by each study.

Limitations

This work involved making assumptions; accordingly, there were areas of uncertainty. While we were able to calculate research expenditures and health gains, determining the strength of the link between the two was not straight-forward. Furthermore, we did not examine CVD risk factors other than smoking, such as obesity and exercise. Finally,

while spillovers have an important role in the dissemination of research, they are difficult to measure precisely.

Conclusion

This analysis will help guide research organizations and policy makers in determining the value of the portfolio of CVD research in Canada. In addition, it will provide valuable insight for other researchers conducting this type of analysis. Finally, this may represent an opportunity to collaborate with other countries in establishing and refining methods to document the value of medical research.

Table 1. Public sector cardiovascular research funding organizations

National Organizations

- Medical Research Council of Canada (MRCC)/Canadian Institutes of Health Research
- The Canada Council/Social Sciences and Humanities Research Council
- Natural Sciences and Engineering Research Council
- Government of Canada, Indirect Costs Program
- Heart & Stroke Foundation of Canada
- Canada Foundation for Innovation
- Canadian Health Services Research Foundation
- Genome Canada

Provincial Organizations

- British Columbia Health Care Research Foundation/Michael Smith Foundation
- Alberta Heritage Foundation for Medical Research (Alberta Innovates - Health Solutions since 2010)
- Saskatchewan Health Research Board/ Health Services Utilization and Research Commission/ Saskatchewan Health Research Foundation
- Manitoba Medical Service Foundation
- Manitoba Health Research Council
- The Physicians' Services Incorporated Foundation
- Banting Research Foundation
- J.P. Bickell Foundation
- Conseil de la recherche en santé du Québec /Fonds de la recherche en santé du Québec
- Nova Scotia Health Research Foundation
- Dalhousie Medical Research Foundation
- Newfoundland & Labrador Centre for Applied Health Research

Table 2. Summary of new users, lifetime health gains (QALYs) and lifetime incremental costs by patient group/intervention (1994-2005).

Patient groups/interventions	Total New User (000s)	QALY gains			Incremental costs		Net monetary benefit (CAD million)
		Unit QALY gained	Total QALYs (000s)	Total monetized (CAD million)	Per new user (CAD)	Total costs (CAD million)	
AMI	**511.3**		**147.3**	**7,365.9**	**53,677.2**	**3,850.4**	**3,515.5**
Fibrinolysis	251.44	0.275	69.15	3457.3	11784.0	2963.0	494.3
Aspirin	46.47	0.213	9.90	494.9	0.0033	0.000152	494.9
Beta blocker	41.78	0.106	4.43	221.4	615.8	25.7	195.7
ACE inhibitor/ARB	29.26	0.740	21.65	1082.7	7704.0	225.4	857.2
Clopidogrel	69.00	0.077	5.33	266.7	999.3	68.9	197.7
Primary PCI	20.15	0.418	8.43	421.4	1.8	0.037035	421.3
Primary CABG	0.32	0.350	0.11	5.5	11684.5	3.7	1.8
Statin	32.06	0.350	11.22	561.0	15991.2	512.6	48.4
Community CPR	9.72	0.417	4.05	202.6	2448.3	23.8	178.8
Hospital CPR	11.10	1.176	13.05	652.5	2448.3	27.2	625.3
ACS	**260.9**		**78.9**	**3,946.8**	**62,069.7**	**1,400.4**	**2,546.4**
Aspirin and Heparin	35.65	0.213	7.59	379.7	0.0033	0.000117	379.7
Aspirin alone	4.25	0.213	0.90	45.2	0.0033	0.000014	45.2
Gp IIB/IIA	19.34	0.099	1.91	95.7	1235.9	23.9	71.8
ACE Inhibitor/ARB	21.82	0.740	16.15	807.4	7704.0	168.1	639.3
Beta blocker	38.63	0.106	4.09	204.7	615.8	23.8	180.9
Clopidogrel	67.01	0.078	5.21	260.4	999.3	67.0	193.5
CABG surgery for ACS	20.18	1.100	22.20	1110.0	35521.6	716.9	393.1
PCI for ACS	28.93	0.418	12.10	605.2	1.8	0.1	605.1
Statin	25.06	0.350	8.77	438.5	15991.2	400.7	37.8
2' Prev Post AMI	**322.9**		**61.2**	**3,062.4**	**10,698.3**	**637.5**	**2,424.9**
Aspirin	81.25	0.213	17.31	865.3	0.0033	0.00027	865.3
Beta blocker	85.77	0.142	12.18	609.0	842.7	72.3	536.7
ACE inhibitor	55.87	0.180	10.06	502.8	2706.8	151.2	351.6
Statin	61.33	0.350	21.47	1073.3	6581.9	403.7	669.6
Warfarin	21.95	0.004	0.09	4.4	147.3	3.2	1.2
Rehabilitation	16.75	0.009	0.15	7.5	419.6	7.0	0.5
Chronic Angina and CHD	**1,491.5**		**555.5**	**27,774.6**	**39,020.4**	**9,066.0**	**18,708.5**
Aspirin in community	580.33	0.213	123.61	6180.6	0.0033	0.001900	6180.6
Statins in community	483.34	0.314	151.77	7588.4	6581.9	3181.3	4407.1
ACE inhibitor	331.51	0.770	255.26	12763.0	15087.0	5001.4	7761.6
CABG surgery	56.10	0.400	22.44	1122.0	11684.5	655.5	466.5
Angioplasty	40.20	0.060	2.41	120.6	5667.1	227.8	-107.2

Table 2. Summary of new users, lifetime health gains (QALYs) and lifetime incremental costs by patient group/intervention (1994-2005) (cont.).

Patient groups/interventions	Total New User (000s)	QALY gains			Incremental costs		Net monetary benefit (CAD million)
		Unit QALY gained	Total QALYs (000s)	Total monetized (CAD million)	Per new user (CAD)	Total costs (CAD million)	
Hospital Heart Failure	**46.0**		**8.5**	**426.1**	**6,857.9**	**42.3**	**383.9**
ACE inhibitor	21.29	0.210	4.47	223.6	37.7	0.8	222.8
Beta blocker	8.51	0.137	1.17	58.3	1368.4	11.6	46.6
Spironolactone	2.38	0.022	0.05	2.6	570.0	1.4	1.2
Aspirin	8.03	0.213	1.71	85.5	0.0033	0.000026	85.5
Statin	5.83	0.193	1.12	56.2	4881.7	28.5	27.8
Community Heart Failure	**410.4**		**77.4**	**3,871.5**	**6,857.9**	**527.4**	**3,344.1**
ACE inhibitor/ARB	175.08	0.210	36.77	1838.3	37.7	6.6	1831.7
Beta blocker	76.30	0.137	10.45	522.6	1368.4	104.4	418.2
Spironolactone	10.38	0.022	0.22	11.2	570.0	5.9	5.2
Aspirin	64.60	0.213	13.76	687.9	0.0033	0.000211	687.9
Statin	84.09	0.193	16.23	811.5	4881.7	410.5	401.0
Hypertension Treatment	**568.7**		**398.1**	**19,903.1**	**1,373.6**	**781.1**	**19,122.0**
All hypertension	568.66	0.700	398.06	19903.1	1373.6	781.1	19122.0
Hyperlipidemia Treatment	**872.4**		**116.9**	**5,845.4**	**10,690.6**	**3,109.0**	**2,736.4**
Statins 1' prevention	761.19	0.134	102.00	5099.9	3563.5	2712.5	2387.4
Gemfibrozil 1' prevention	83.45	0.134	11.18	559.1	3563.5	297.4	261.7
Niacin 1' prevention	27.82	0.134	3.73	186.4	3563.5	99.1	87.2
Heart Transplant	**2.0**		**2.9**	**145.5**	**68,287.4**	**134.7**	**10.8**
Heart Transplant	1.97	1.475	2.91	145.5	68287.4	134.7	10.8
Smoking	**467.5**		**767.0**	**38,347.5**	**111.9**	**420.8**	**37,926.7**
Smoking cessation	220.28	0.990	218.08	10903.9	111.9	420.8	10483.1
Smoking nonstarting	247.24	2.220	548.87	27443.6	0	0	27443.6
Total	**4,953.6**		**2,213.8**	**110,688.8**		**19,969.6**	**90,719.2**

Legend:

QALY – Quality Adjusted Life Year
CAD – Canadian Dollars
AMI – acute myocardial infarction
ACS – acute coronary syndrome
CHD – cardiovascular heart disease
ACE – angiotensin-converting enzyme inhibitor
ARB – angiotensin receptor blocker
PCI – percutaneous coronary intervention
CABG – coronary artery bypass surgery
CPR – cardiopulmonary resuscitation
Gp IIB/IIA – glycoprotein IIb/IIIa

Note: Studies used to generate QALYs and costs are included in references 13-54.

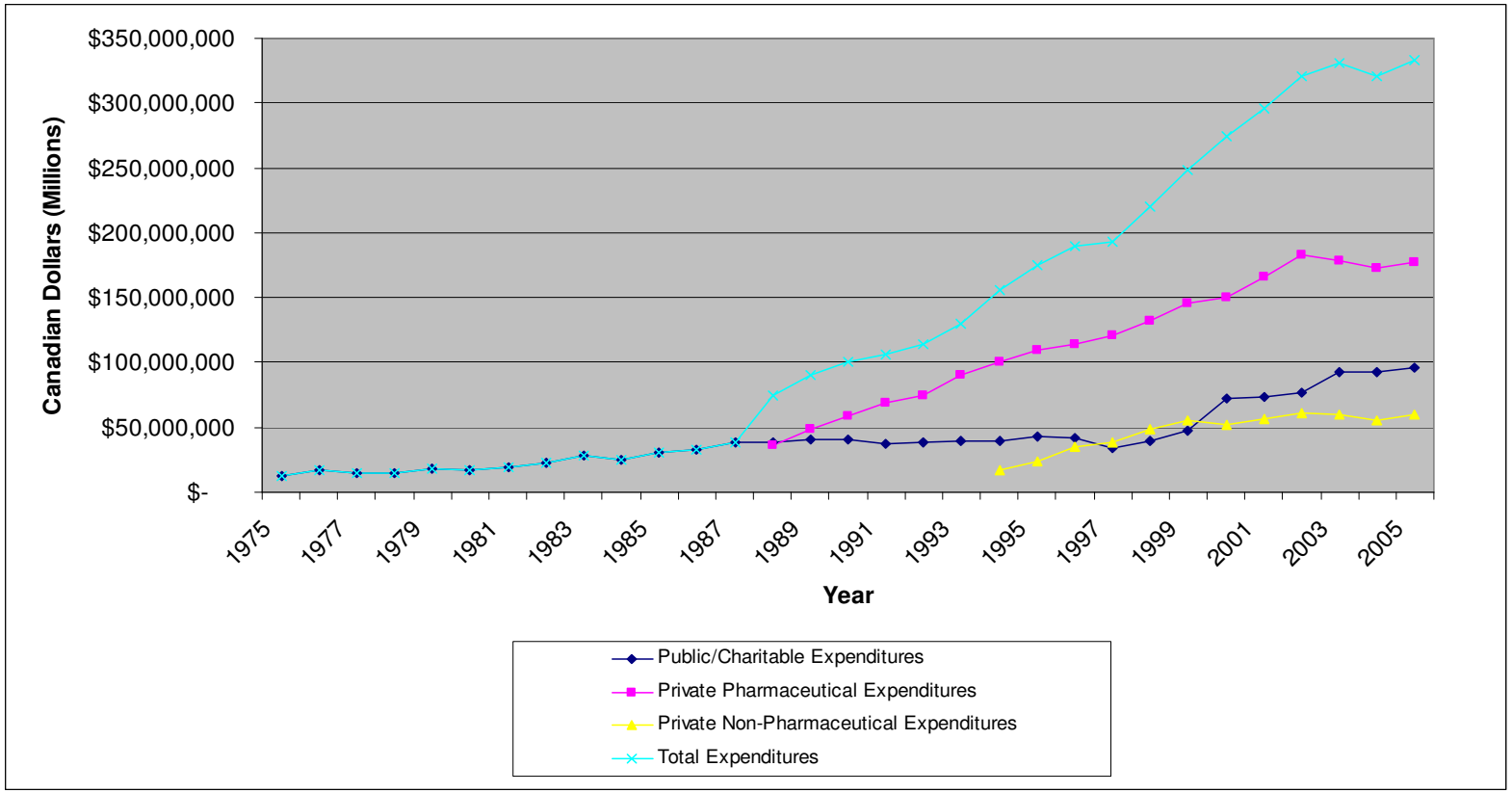
Table 3. Estimates of the input parameters, the internal rate of return, benefit-cost ratio and return on investment for Canada and the United Kingdom.

	Canada			**United Kingdom** (Buxton et al.'s report)		
	Baseline	Optimistic	Pessimistic	Baseline	Optimistic	Pessimistic
Input Parameter Estimates						
Time lag	13 years	10 years	17 years	17 years	10 years	25 years
QALY value	$50,000	$60,000	$40,000	£25,000	£30,000	£20,000
National contribution	6%	8%	4%	17%	25%	10%
Medical research contribution	0.7	1	0.5	1	1	1
Research expenditure	X	X	125% * X	Central	Low	High
Internal Rate of Return Estimates (%)						
Point time lag case	20.6	35.1	10.3	9.2	22.5	Negative
Distribution time lag case	20.6	35.0	10.0	n/a	n/a	n/a

Legend:

QALY – quality-adjusted life-years
X – represents our estimate of research expenditures
n/a – not available

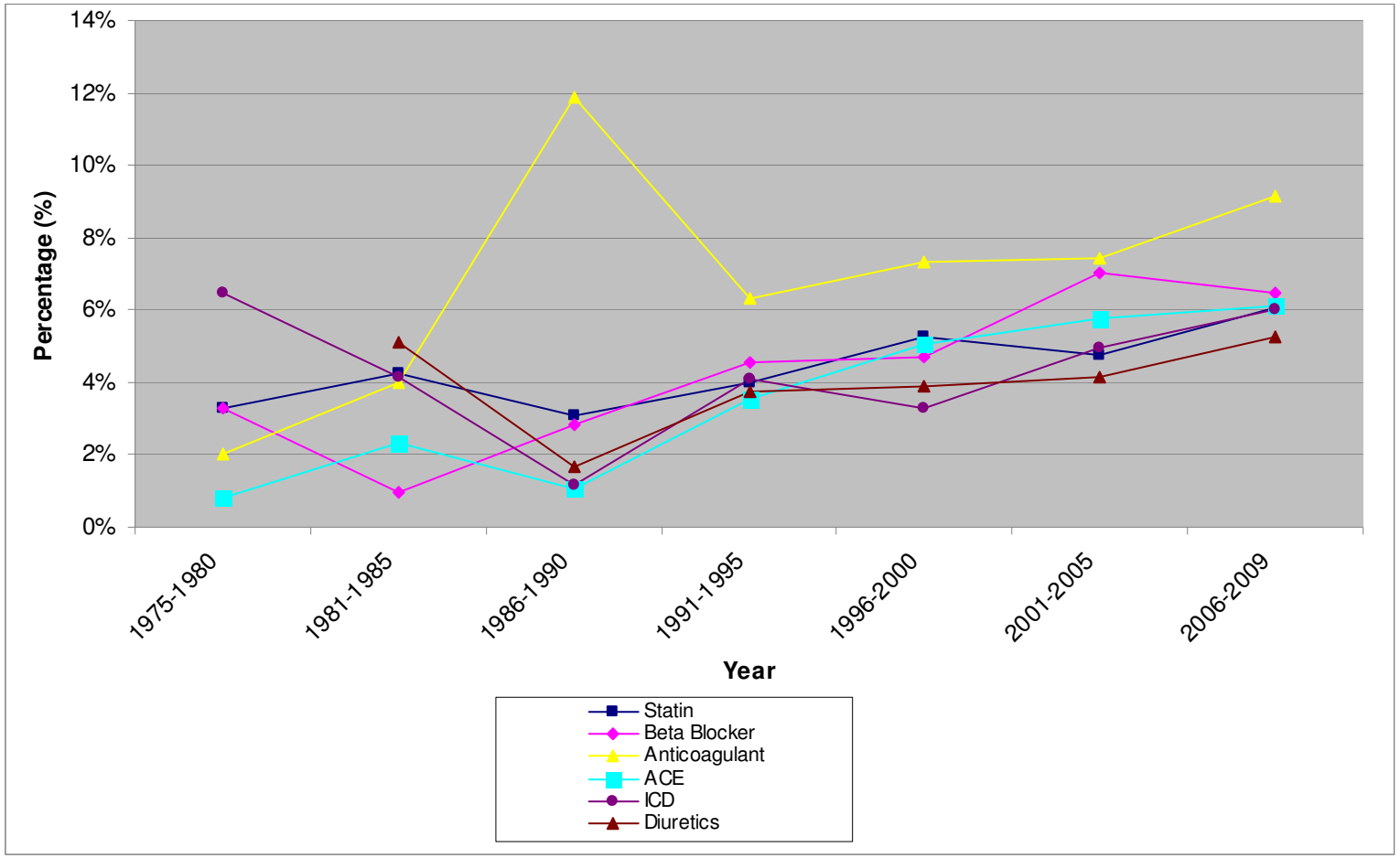
Figure 1. Total expenditures on cardiovascular R&D in Canada by source, 1975-2005.



Source: Medical Research Council of Canada reference lists and annual reports of public/charitable organizations; authors' calculations based on data from the Patented Medicine Prices Review Board 2008 Annual Report (http://www.pmprb-cepmb.gc.ca/english/View.asp?x=91&mp=68); authors' calculations based on data from Statistics Canada CANSIM Table 358-0024 "Business enterprise research and development (BERD) characteristics, by industry group based on the North American Industry Classification System, annual (dollars unless otherwise noted)", retrieved on Thursday October 14th 2010; base year: 2005.

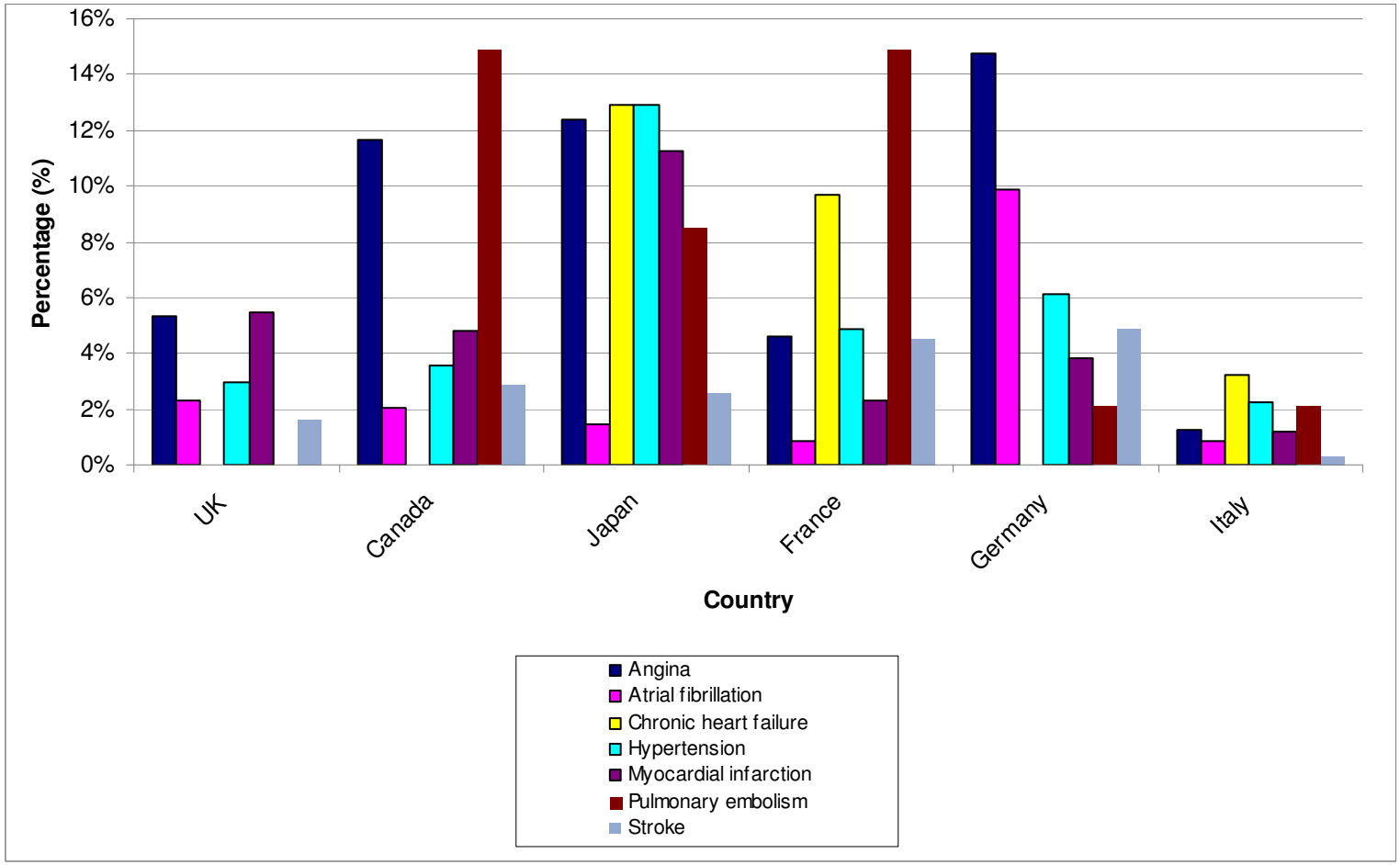
NB: Data for the private pharmaceutical and non-pharmaceutical sectors only available from 1988 and 1994 onwards, respectively.

Figure 2. Trends in Canadian contribution in global research by cardiovascular disease category.



Source: Authors' calculation using data from Web of Science.

Figure 3. Contribution of G7 countries to the world's pool of patents in 7 cardiovascular disease guideline areas.



Source: Canada patent database (1978-2008).

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Appendix

Methods

Our approach adhered closely to the model suggested by Buxton et al. (1), while incorporating an existing model, the Ontario IMPACT model (2), which characterizes changes in the burden of CVD between 1994 and 2005 in Ontario. Our main objective was to estimate the return obtained from investing in CVD research, that is, the internal rate of return (IRR) for public/charitable CVD research.

In order to calculate our measure of return, we estimated the following elements:

a) expenditures on CVD research from the public/charitable sector
b) health gains and costs from new CVD treatments and procedures
c) proportion of health gains attributable to CVD research and Canada's contribution to overall research
d) time lag between research expenditures and health gains
e) R&D spillovers from public/charitable sector investments

Our first step was to estimate the magnitude of past spending on cardiovascular research for the public/charitable sector from 1975 to 2005; we also calculated expenditure estimates for the private sector (pharmaceutical and non-pharmaceutical industries).

Estimates of public/charitable sector funding

To obtain data on expenditures of public/charitable-funded research by the major public/charitable funding bodies, we compiled a list of national granting agencies, such as

the Canadian Institute for Health Research, the Natural Sciences and Engineering Research Council and the Social Sciences and Humanities Research Council, and the major foundations, such as the Heart & Stroke Foundation of Canada, the Canada Foundation for Innovation; and other provincial organizations. Next, we undertook a comprehensive internet search for additional organizations. Finally, we made use of the Reference Lists of health research in Canada (which include data collected by the former Medical Research Council of Canada) to provide us with names of organizations that were not captured in our search, either because they no longer exist or have changed their name over the years.

Once a list of organizations was compiled, we contacted every organization to obtain cardiovascular-related expenditures from 1975 to 2005 (Table 1). Information was provided either directly by the organization or obtained through its annual reports or the reference lists. In particular, we scanned the grant and fellowship/scholarship titles (and summary/key words, when available) to assess their suitability for inclusion in our analysis. The grants and fellowships/scholarships were included if the clinical conditions studied included heart and peripheral vascular diseases.

Estimates of private sector funding

We also estimated past research expenditures for the private sector. This sector consists of the pharmaceutical and non-pharmaceutical industries. Pharmaceutical and medicine research and development (R&D) includes pharmaceutical and medicine manufacturing, pharmaceutical wholesale trade and pharmaceutical scientific R&D services, while non-

pharmaceutical R&D includes testing laboratories and health care and social assistance industries (3). We used various sources to obtain data on research funding in this sector; however, the lack of detailed data required making some assumptions.

In particular, to obtain expenditures data on cardiovascular research for the pharmaceutical industry, we used published data from the Patented Medicine Prices Review Board (PMPRB) (4). Disaggregated data by individual therapeutic area were not available; furthermore data were only available from 1988 onwards. Based on previous work on this topic (1, 5), we employed a conservative estimate that 15% of all pharmaceutical research expenditures were spent on cardiovascular research.

Data on R&D spending by the private non-pharmaceutical health care sector are even scarcer than for the pharmaceutical sector and represent a small percentage of total expenditures. We used Statistics Canada's data, although these were not sufficiently disaggregated to obtain exact figures. Data were only available from 1994 onwards. For the private, non-pharmaceutical R&D sector, we focused on the Health Care and Social Assistance sector as it is more representative of the non-pharmaceutical health care sector. Again, we assumed that roughly 15% of all expenditures were spent on cardiovascular-related research. For each funding sector, we estimated the value of expenditures in both current and constant dollars, adjusted by the Consumer Price Index to 2005 dollars.

Our next step consisted of estimating the magnitude of health gains and costs associated with new CVD treatments between 1994 and 2005. This required the following sub-steps:

1) Estimate the number of individuals receiving cardiovascular treatments (because many patients with CVD received more than 1 treatment, we had to determine accurately the number of unique users for each treatment)
2) Determine the magnitude of health gains associated with each new treatment, expressed in QALYs
3) "Monetize" the health gains

Estimate number of individuals receiving cardiovascular treatments

To estimate the number of unique users for different interventions to treat or prevent cardiovascular heart disease from 1994 to 2005 in Canada, we made use of the Ontario IMPACT model (2). Our approach can be described in five steps:

a) Identify interventions and patient groups
b) Estimate the numbers of patients in each patient group
c) Estimate the uptake of each intervention by each patient group
d) Compute the number of users of each intervention in each patient group (by multiplying the values obtained in steps b) and c)
e) Compute the number of unique users for each intervention in each patient group

We identified interventions and patient groups through the Ontario IMPACT model (2). In particular, we examined nine mutually exclusive groups eligible for cardiovascular treatment - acute myocardial infarction (AMI), acute coronary syndrome; post-AMI

survivors; chronic angina and cardiovascular heart disease; hospital heart failure; community heart failure; hypertension; hyperlipidemia and heart transplant – as well as smoking cessation. Within each of these groups, a total of 47 medical and surgical therapies were assessed (Table 2). We scaled up the numbers of patients in each patient group using accurate population data obtained from Statistics Canada (6) by population weights. High quality data were only available for six time points (1994, 1995, 1996, 2004, 2005, and 2006). Linear interpolation technique was used to estimate data for missing time points.

To estimate the number of unique users for each intervention in each patient group, we made use of Buxton et al.'s work (1). In their analysis, the authors computed the number of unique users in each year by subtracting the number of users in each year from the number of users in the previous year, while accounting for the number of deaths from all causes among users in the previous year. This approach assumed that patients in each patient group would remain in the same patient group for their life year. We relaxed this assumption and employed three different methods to estimate the number of unique users for each intervention in each patient group.

1. For medications that were likely to be used on a long-term basis (for example aspirin, ACE-inhibitors and β-blockers), we developed a new method to estimate accurately the number of unique users per year.

   First, we estimated the total number of users for each intervention across all patient groups for each year based on the result from step d). For example, in

1995, there were 1,784,031 patients across the disease states, with 628,955 (35.3%) on aspirin (ASA) (35,561 in AMI; 31,764 in ACS; etc).

Next, we estimated the number of new users per year for each intervention for all patient groups. To do so, we calculated the difference in users for each year compared to the previous year, while accounting for users who died. For example, of the patients on ASA in 1995 (628,955), 0.3% died. Therefore, 627,068 patients on aspirin survived until 1996. We assumed they remained on aspirin.

Lastly, surviving patients on a particular therapy, such as aspirin, were distributed across the different disease states: some in the AMI group, others in ACS and others in HF. We distributed the surviving users from a previous year into the appropriate patient groups in the current year, using the same distribution of patients as in the current year. For example, in 1996, of the total 631,399 patients on ASA, 5.0% were in AMI, 3.2% were in ACS. We assigned the surviving ASA users from 1995 to the 1996 groups in a similar fashion. Therefore, 216[1] unique ASA users were counted in the 1996 AMI disease category. This process was applied to all chronic treatments, such as aspirin, β-blockers, angiotensin-converting enzyme inhibitors, statins and warfarin. This method allowed for patients to transition between patient groups.

2. For acute in-hospital therapies (PCI, CABG, fibrinolysis, CPR, heparin, GP IIb/IIa, clopidogrel, and angioplasty), we assumed that the number of total users was equal to the number of unique users.
3. For hypertension and hyperlipidemia treatments, we used the Buxton et al. (1) approach to calculate the number of unique users. We computed the number of

[1] (Total ASA 1996 – Total Survive ASA 1995) * ASA in AMI ratio = (631399 – 627068)* 0.05 = 216

unique users in each year by subtracting the number of users in each year from the number of users in the previous year, while accounting for the number of deaths from all causes among users in the previous year.

Table 2 summarizes our results.

Next, we examined two channels through which medical and CVD research reduced smoking: (i) encouraging smokers to quit; and (ii) discouraging young people from starting smoking. To estimate the number of individuals for each category, first we calculated the number of quitters and non-smokers and then estimated the proportion of these numbers that could be attributed to the influence of medical/CVD research. To calculate the number of quitters and non-smokers, we used data from the National Population Health Survey (1995-1998) (7) and the Canadian Community Health Survey (2000-2005) (8). To estimate the proportion of quitters and non-smokers due to the influence of medical/CVD research, we made use of the Canadian Tobacco Use Monitoring Survey (CTUMS) (9). The CTUMS asked former smokers why they quit smoking; about 30% stated they the main reason they quit was because they were worried about the future (9). We assumed 70% of smokers' concern about future health was informed by medical/CVD research. The proportion of individuals who quit smoking due to medical/CVD research was thus estimated to be 21% (0.3 * 0.7). For non-starters, we assumed that medical/CVD research accounted for 20% of non-starting decisions among young people.

Determine magnitude of health gains associated with each new treatment, expressed in QALYs

A systematic review of the economic literature was performed to obtain estimates of the QALYs gained for each intervention over a lifetime horizon (10-51). Studies were obtained through Pubmed[2]. In addition, the references of papers that were retrieved were searched. We first searched for papers that most accurately reflected the specific intervention considered and the specific patient group to whom the intervention was offered in Canada. Whenever possible we used Canadian studies to reflect Canadian practice patterns and costs. Studies that compared the intervention to placebo or standard of care were preferred. When an economic evaluation was not available for a particular patient group or intervention, estimates of a patient group that was most closely related to the patient group of interest was used. If a QALY estimate was not available for a particular intervention, we calculated the QALY gain using the incremental life expectancy gain and the utility estimate for the most relevant health state. Articles that incorporated a lifetime time horizon were preferred. There was no single discount rate used by all studies and we did not adjust for the differences in discount rates of each of the studies.

The marginal lifetime cost for each health care intervention was also collected from the same systematic search. When possible, cost estimates were obtained from the same paper; Canadian costs were preferred. When these were not available, we used non-Canadian studies and converted the costs to Canadian dollars using the Purchasing

[2] http://www.ncbi.nlm.nih.gov/pubmed/

PowerParity[3]. All costs were inflated to 2005 Canadian dollars using the Consumer Price Index from Statistics Canada. The estimates for QALY gains and the incremental costs can be found in Table 2.

To estimate QALY gains and costs associated with each smoking quitter, we relied on a study by Wang et al. (48). This study undertook a systematic review of the effectiveness of nicotine replacement therapies in smoking cessation and estimated their cost-effectiveness. Wang et al. reported QALY gains for quitters at different ages; we used the value of 0.99 QALYs gained for the age group 55-64 from their study. This study did not include an estimate of the QALY gains associated with smoking deterrence but the authors reported a gain of 2.22 QALYs from quitting smoking for the under-35 age group. We used this value as the QALY gain estimate for a nonstarter. In terms of the costs of quitting, we used the cost estimate provided by Wang et al., $119 CAD per smoker. For nonstarters, we assumed that there was no cost involved. These costs are likely an overestimate, as they do not include cost savings from reduced health care use associated with successful quitting or deterrence.

"Monetize" health gains

Having obtained the QALY gains for CVD interventions as well as for quitting smoking and smoking deterrence, we then converted these QALY gains into monetary values by multiplying the QALY gains by the monetary value of a QALY. We assumed that one

[3] http://www.oecd.org/department/0,3355,en_2649_34357_1_1_1_1_1,00.html

QALY was worth $50,000[4] in our baseline estimate. In our optimistic scenario calculation, we assumed that one QALY's value was $60,000, and in the pessimistic scenario, $40,000. With the monetized QALY gains and net health care costs, we then calculated the net monetary benefit for each CVD interventions by deducting the net health care costs from the monetized QALY gains. Thus, this net monetary benefit metric attached a monetary value to net health benefit of CVD interventions.

The next steps involved determining the "link" between expenditures and health gains; in particular, required ascertaining: 1) whether the health gains realised could all be attributed to the medical research undertaken or whether part of it was due to other types of research or non-medical factors, such as income, housing conditions, etc or even knowledge exchange and translation activities (attribution issue); 2) how much of these gains were due to the Canadian research expenditures as opposed to research conducted elsewhere (Canadian contribution); and 3) from the moment research expenditures were made, how long it took for them to translate into health gains. Beyond the health gains, medical research can also produce economic gains, that is, the social return from undertaking medical research; we also estimated this value.

We examined the social determinants literature to assess their effects on improvements in cardiovascular health. The literature suggests that between 32% and 56% of the variation in health outcomes in Canadians is explained by social and economic factors (54).

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[4] This is comparable with the QALY value in Buxton et al (3) (£25,000); however, this is a conservative value compared to recent studies which have used a value of $100,000 per QALY (52, 53).

Bunker (55) estimated that half of the 7.5 years of increased life expectancy since the 1950s can be attributed to medical care.

To estimate the proportion of global health gains attributable to Canadian CVD research, we used two approaches: a bibliometric search and the use of patent data. The first approach used published data, and estimated the Canadian contribution to global CVD research by determining the proportion of research publications that are Canadian. The data were obtained from Web of Science and included all type of publications. We categorized search results by country of primary author. The second approach made use of patent data (which tend to be for drugs and devices). We analysed data on the number of patents by country of ownership. We assumed that the Canadian contribution to world research in CVD could be approximated by the proportion of Canadian patents in CVD issued within the world pool of CVD patents. We conducted an internet search of the databases of Canadian Patents[5], the US Patent and Trademark Office, and the Canadian Intellectual Property Office[6]. Search terms were similar to those used in the bibliometric method. The main difference was that search engines available in the two patent databases allowed us to specify the country of patent ownership before starting our search. We scanned through detailed descriptions of each patent in the search results to select only patents relevant to CVD.

Then, we examined the time required to reap the clinical benefits of research funding-that is, the time lag between research expenditures and health gains obtained. Because

[5] http://brevets-patents.ic.gc.ca/opic-cipo/cpd/eng/search/advanced.html
[6] http://patft.uspto.gov/netahtml/PTO/search-adv.htm

future benefits are discounted, very long time lags can result in a poor return on investment for health research. Conversely, short time lags may frame health research in a more favourable light. The time lag can be defined as the interval between the time research was done (date of first publication of first patent could be used as a proxy) and the time when the clinical benefit was achieved (date at which findings appear in clinical literature that can be used as a proxy for average time of uptake in time lag studies). To determine an appropriate time lag factor, we reviewed the literature to assess the existing approaches to estimate time lag (56, 57).

Beyond the health gains discussed beforehand, medical research can produce economic gains. In this last step, we estimated the magnitude of economic gains (social return) that are generated by public/charitable sector sponsorship of cardiovascular medical research in Canada. In other words, we sought to estimate the additional national income that was generated from publicly/charitably funded medical research in Canada. To quantify the non-health gains obtained from research, we estimated the spillover that occurred from undertaking research, i.e., the "benefit" or return that a given firm/organization obtains because of research and development (R&D) undertaken by other firms/organizations. We employed two approaches to estimate this return using values from the existing literature. In the first approach, the 2-stage approach, first we estimated the private R&D stimulated by public/charitable research, and second we estimated the social rate of return to private R&D stimulated by public/charitable R&D. In the second approach, the 1-stage approach, we estimated directly the social rate of return on public/charitable research

generated by all transmission mechanisms. See Buxton et al (1) for a detailed description of each approach.

Finally, the estimates from the previous steps were brought together to compute the economic returns on public/charitable research expenditure for CVD by calculating the internal rate of return (IRR). The IRR can be described as the annual rate of return such that the net present value of all cash flows (both positive and negative) from a particular investment equals to zero (i.e., the interest rate that makes the present value of future returns equal to the present value of the current investment) (see formula)). For example, if the IRR = 10%, this means that a $1 invested in research will yield returns of $0.10 per year in perpetuity.

$$\left(\frac{\left[\sum_{t=1994}^{2005} (MG - IC) \right] \times Can.cont \times Medical.cont}{IRR^{Timelag}} \right) - \left(\sum_{t=1994-Timelag}^{2005-Timelag} (Expenditure) \right) = 0$$

Generally, an investment is considered acceptable if the IRR is greater than an established minimum rate of return (hurdle rate) or cost of capital. In the private sector, most firms use a 12% hurdle rate as the minimum; this value is based on returns of the S&P 500[7], which are typically somewhere between 8% and 11% (annualized). The IRR is readily comparable to interest and discount rates.

[7] The S&P 500 is a stock prices index of the 500 largest companies in leading industries of the US economy. (http://www2.standardandpoors.com/spf/pdf/index/SP_500_Factsheet.pdf).

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