The Economic Contribution of Industry-Sponsored Medical Device Clinical Trials to Health Care and Health Research in Alberta

by

Ayse Ilke Akpinar

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ABSTRACT

Background: Although the clinical research in devices has been growing in importance, very little is known regarding their full economic contribution; such as the market price of the device, all clinical services and administrative activities of industry-sponsored medical device trials.

Purpose: To document the economic value of industry-sponsored clinical studies for medical devices provided to Alberta, Canada.

Methods: We used the Northern Alberta Clinical Trials and Research Center data to identify all industry-sponsored medical device clinical trials initiated in Northern Alberta from 2012 to 2016. For each trial we calculated the cost of devices provided by the sponsor and the cost of clinical and administrative services that were incurred to operationalize the device clinically. Operationalizing the device within the clinical study abrogates the need for the public payer to carry this cost. We extrapolated these results to all trials in Alberta based on information obtained from the registration website *ClinicalTrials.gov*.

Results: Our sample consisted of 23 device trials which were initiated between January, 2012 and January 2016, and followed up until January 2018. The monetary value of the industries' contribution was C$368,261 per trial. Devices accounted for 55% of the total contribution of this cost. Extrapolated, the total province-wide contribution was estimated to be C$18 million. This benefit to society would be paid for publicly without the medical device clinical study.

Conclusion: Economic aspects of industry-sponsored CTs for medical devices has been largely ignored. As economic evaluation activities grow in importance, it will be important to recognize the economic aspects of clinical studies of medical devices, including those resulting in savings to public and private sectors. The monetary values presented in this study can inform the creation of

new financial and regulatory public policies, and encourage health regions to strengthen their market in collaboration with industry partners.

PREFACE

This thesis is an original work completed by Ilke Akpinar. The project plan was reviewed by the University of Alberta Health Research Ethics Board and did not require ethics approval because it used only secondary data.

This thesis work has been submitted for publication as an article: "Akpinar I, Ohinmaa A, Thording L., Tran D, Fedorak R, Richer L, Jacobs P. The Economic Contribution of Industry Sponsored Medical Device Clinical Trials to Health Care and Health Research in Alberta. *International Journal of Technology Assessment in Health Care* on July 26, 2018.*"* Richard Fedorak and Philip Jacobs conceptualized the study. I was responsible for data analyses and manuscript compositions. L. Richer and L.Thording provided the data. All authors contributed to the writing of the manuscript and critically reviewed the manuscript for intellectual content.

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LIST OF ABBREVIATIONS

AB	Alberta
AHS	Alberta Health Services
C$	Canadian Dollars
CBER	Center for Biologics and Evaluation Research
CDRH	Center for Devices and Radiologic Health
CIHR	Canadian Institutes of Health Research
CT	Clinical Trial
FD&C Act	Federal Food, Drug and Cosmetic Act
FDA	Food and Drug Administration
GAO	Government Accountability Office
HDE	Humanitarian Device Exemption
IDE	Investigational Device Exemption
IRB	Institutional Review Board
MeSH	Medical Subject Headings
NACTRC	Northern Alberta Clinical Trials and Research Center
NEST	National Evaluation System for Health Technology
OECD	Organisation for Economic Co-operation and Development
PMA	Pre-market Approval
PMN	Pre-market Notification
PPP	Purchasing Power Parities
RCT	Randomized Controlled Trials
SUD	Single Use Device
UDI	Unique Device Identifier

Chapter 1: INTRODUCTION

Eleven percent of Canada's gross domestic product was spent on health care in 2017, and it was around $242 billion (1). Although it is not well tracked, it is estimated that 3% of this annual budget spend for the medical devices (2). The demand for medical devices have been increasing. Ageing population and medical device innovation are the main factors for the increased demand (3).

Clinical trials are important components in the licensing of medical devices. In the United States, the Food and Drug Administration (FDA) requires manufacturers to conduct clinical studies to obtain a Premarket Approval (PMA) for Class III devices. Clinical studies include randomized trials and other studies based on observational data to which data on device identifiers and use have been attached. Many of these studies have been sponsored by device manufacturers; they also contribute directly to patient care, as they divert patients from the routine funding stream of care, which is both public and private.

Although there are studies which document the economics of clinical research, most of these are for pharmaceuticals or medical and surgical procedures (4-7). The research, development and approval process is much more developed for drugs than medical devices. However, clinical research in devices - including its economic components- has been growing in importance. According to the U.S. National Library of Medicine database, *ClinicalTrials.gov*, the number of medical device trials that were started almost tripled from 51 in 2005 to 139 in 2015 (8). Even though the FDA does not require economic data in its PMA submissions, the rapid growth of expenditures on a variety of medical devices (3) calls for a greater degree of economic considerations in clinical studies.

The purpose of this study is to document the economic characteristics of clinical studies for medical devices using a clinical trial database in Northern Alberta.

1.1 Definition of Medical Device

The term "medical device" applies to everything from simple tools used for medical examinations, such as tongue depressors and latex gloves, to life-saving implantable devices like cardioverter defibrillators and biliary stents. Medical Device Amendments section 21 U.S. Code 321(h) of the FD&C Act (Federal Food, Drug, and Cosmetic Act) provides the definition of "medical device" as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is recognized in the official National Formulary, or the United States (U.S.) Pharmacopeia, or any supplement to them; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes." (9).

A wide variety of medical devices can be classified according to their technological advancement level (e.g., conventional and advanced), their departmental usage (e.g., cardiovascular, orthopedic, radiologic), their degree of invasiveness (e.g., invasive, minimally invasive, non-invasive), or their connection level and degree of integration with the body (e.g., implantable, injectable drug delivery device, centrally inserted external use, extracorporeal usage, external use, wearable). We can also group them based on the number of uses (e.g., multiple use, reprocessable single-use device (SUD), and non-reprocessable single use device) and for the number of patients who can

use them (one-person use, more than one person, public use) and based on their purpose (e.g., screening, monitoring, diagnosis, prevention, treatment, rehabilitation) (Table 1-1).

1.2 U.S. FDA Medical Device Classification and Regulation

Although Food and Drug Administration (FDA) has had the responsibility to regulate the drugs' safety and efficacy since 1938, the agency's role was expanded, and includes oversight of safety for medical devices with the Federal Food Drug and Cosmetics Act in 1976 (10). The Center for Devices and Radiologic Health (CDRH) and the Center for Biologics Evaluation and Research (CBER) are responsible for regulating medical devices. There are three types of processes to obtain FDA approval for medical devices. These are the Pre-market Approval (PMA) process, the Pre-market Notification (PMN) process, and the Humanitarian Device Exemption (HDE) process.

In the U.S., the medical device research and innovation process is complex due to the strict regulatory requirements and wide variety of devices. The FDA categorizes devices into three classes according to the risk associated with their intended use (11) (Table 1-2). Devices are classified according to the type of regulatory process needed. Forty-seven percent of devices (e.g., stethoscopes, enema, elastic bandages) fall into class I category. Most of these are considered low risk, so they only need "general controls". Before marketing the class I device, manufacturers must register the device with the FDA (12).

Class II medical devices (e.g., computed tomography scanners), which comprise 43 percent of all devices, bear some or unknown risk. For a class I, II, and III device for which a PMA application is not required, a manufacturer must submit a PMN or 510(k) to the FDA unless the device is exempt from 510(k) requirements of the FD&C Act. The producers do not have to prove that the devices are safe and effective, but they must demonstrate that a new device is "substantially

equivalent" to another device which is already on the market (13). There are exemptions and some class I and class III devices also use the 510(k) process (14).

A class III device (e.g., heart valves, implantable cardioverter-defibrillators) is one with a higher or unknown risk, and about 10 percent of devices fall into this category. The manufacturer must apply for PMA, and the application should include clinical evidence of safety and effectiveness (15). Some class III devices called predicate devices, have only minor differences from the devices already approved, and do not require rigorous testing. Before submitting a PMA application, the manufacturer must apply for an Investigational Device Exemption (IDE) (16). An IDE approval allows the manufacturer to use the device in clinical trials to create the safety and effectiveness data for the PMA application (14).

Humanitarian use device is one that is expected to treat or diagnose conditions that affect less than 4,000 individuals in the U.S. and the HDE process differs from the PMN and PMA pathways. First, HDE needs a demonstration of device safety, but not device efficacy. Second, the use of a humanitarian device requires supervision and approval by the local institutional review board (IRB). Finally, within the FDA, the Office of Orphan Products Development is responsible for humanitarian device regulations (17).

The U.S. FDA made substantial changes to medical device regulation in 2016, and set up the priority review program for devices targeting diseases with no approved alternatives are available. In December 2016, The U.S. House of Representatives passed the 21st Century Cures Act (18), which permits certain medical device approvals without conducting randomized clinical trials. If a device needs a confirmatory study to support a PMA, observational studies and "clinical experience'' showing that the device is "safe and effective" are also accepted by the FDA (15).

Post-market surveillance is also an important part of medical device regulations, mostly because it is difficult to collect safety and effectiveness data for medical devices before market entry. Health care centres are required to report any adverse events to the manufacturer and the FDA. Currently, the FDA is establishing the National Evaluation System for Health Technology (NEST) incorporating unique device identifiers (UDI) into electronic health records. This is expected to decrease the need to conduct post-market surveillance studies and to make the safety and effectiveness data more reliable and accessible (19).

Medical devices can change quickly, and the improved version might be in development during the early market stage or even the clinical development stage of the previous version. Most medical devices are replaced by a newer version every 18 to 24 months (20). Due to the rapid evolution of technology and relatively short lifetimes of the medical devices, medical device companies are less reliant on patents compared to pharmaceutical companies (21). Besides, manufacturers only profit from the attractive margins of the new products, until the patents disclose the innovation details, and provides incentives for competitor companies to produce the improved versions of the existing devices.

1.3 Health Canada Medical Device Classification and Regulation

Health Canada is the federal regulator of medical devices, and The Medical Devices Bureau of the Therapeutic Products Directorate is responsible for licensing medical devices (22). Health Canada does not have a specific definition of medical device, and they use the U.S. FDA definition of the medical device on their webpage. Similar to the U.S. FDA, medical devices are regulated according to a risk-based classification system in Canada, but under this classification scheme they

have four classes. Class I devices represent low-risk items, while classes II-IV represent higher-risk devices (23) (Table 1-3).

Device classification dictates the type of license required for the device, as well as quality management system requirements. Class I (e.g., nasal aspirator, nasopharyngeal airway, adhesive strip) devices do not require a medical device license and are monitored through medical device establishment license (MDEL). Class II (e.g., biliary stone retrieval basket, bronchoscope, endoscopic camera), III (e.g., computed tomography, hemodialysis catheter, cochlear implant), and IV (e.g., cerebrospinal catheter, cardiac defibrillator, heart valve) devices require a product-specific Canadian Medical Device License (MDL) and ISO 13485:2003 or ISO 13485:2016 certification. While Class III device applications are based on the submission of summary documents, class IV device applications are based on extensive data—such as evidence of effectiveness from clinical studies (24, 25).

1.4 Definition of Clinical Trials

The U.S. FDA defines clinical trials (CT) as "voluntary research studies conducted in people and designed to answer specific questions about the safety and effectiveness of drugs, vaccines, other therapies, or new ways of using existing treatments." (26).

According to Canadian Institutes of Health Research (CIHR), the CT is "A prospective controlled or uncontrolled research study evaluating the effects of one or more health-related interventions assigned to human participants." (27).

1.5 Medical Device Clinical Trials

Similar to drug trials, the medical device CTs also bring benefits to the health regions, with their impact on the scientific knowledge, provision of high-quality medical care, and also with their contribution to both public and private funding stream of healthcare. On the other hand a medical device CT design differs from the drug trial design. Randomization is not common for medical device CTs which are usually conducted with smaller "pilot" patient populations. Due to ethical considerations and clinical needs of the patients, it is not common to use placebo or sham control for medical device CTs. It is also difficult to ensure blinding to the individuals or the investigators in a device trial (28). Medical device CTs do not have traditional endpoints. They are specifically designed to generate endpoints to meet the approval requirements of the directive of the regulatory agencies. On the other hand, the study must meet multiple regulatory requirements to gain market access in different countries (29).

Medical device trials can be grouped into three categories: pilot studies, pivotal studies and post-marketing studies. ***Pilot*** studies are conducted using smaller populations with diseases or conditions (fewer than 100 individuals) and are often limited to a single center or a few centers. These studies aim to determine preliminary safety and performance information about the device's use in humans before a larger-scale clinical study is launched. ***Pivotal*** studies recruit more patients than pilot studies (up to 1,000 individuals). They are designed to test specific hypotheses that support PMA application submissions for premarket 510(k) notifications if effectiveness and adverse effects data are needed to establish substantial equivalence. ***Post-marketing*** studies are often required as approval conditions for PMAs. These studies aim to document adverse effects and collect long-term data on specific safety and performance factors (30, 31).

1.6 Importance of Clinical Trials

CTs provide safety, efficacy, effectiveness and cost-effectiveness data on healthcare interventions. All these measures are important for policymakers and also for reimbursement decisions. They contribute to research capacity building by attracting high-quality clinical personnel to the research centres, and as a result, patients can get high-quality health care. Awaiting patients also can potentially obtain access to new and better ways to detect and treat their diseases through CTs before the treatment is available in the public system. Healthcare services, investigational drugs and devices are also provided to participants without waiting lists or co-payments.

Canada spent C$500.9 million on applied research (pre-clinical and clinical) in 2016. Clinical trials accounted for 72% of this expenditure (32). Research and development funding bodies encompass public sector (government), private sector (charities and industry) and international funding (multinational projects and international funders) (Figure 1-1) (33). Since the sponsoring industry began to cover the clinical services and provide the devices and drugs free of charge, CTs have started to play an important role in healthcare management and budgets. Without CTs, all these expenses would have to be funded through government, private insurance, and patients.

1.7 Literature Review

We conducted a literature review to provide the current information about the economic value of industry-sponsored device related CTs to the regional or national economy. We performed a literature search using a combination of subject headings and keyword terms in Medline (EBSCO version). The search was conducted on June 8, 2018. All search strategies were developed using expertise of University of Alberta Research Librarian. MeSH (Medical Subject Headings) terms or keywords used in the literature search were medical device, equipment and supplies, economy

(regional or provincial or federal or national), economic (contribution or impact or value). We did not use any methodological filter and we did not limit the search by year or language. Appendix 1 shows the detailed search strategy.

We identified 50 potentially relevant articles. Search results were screened first by title and abstract, then, in the final screening process by the full-text review. A flowchart of the study selection process was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Figure 1-2) (34). Studies available in the literature mostly focus on the cost of the intervention, not the description of the costs of the trial. There was no publication that evaluated the medical device costs avoided through conducting industry-sponsored CTs or the full economic contribution (market price of the CT device, all clinical services and administrative activities) of industry-sponsored medical device CTs.

1.8 Study Objective

The purpose of this thesis is to estimate the economic contribution of the industry-sponsored medical device CTs on a provincial basis in Alberta, Canada. This study estimates the contribution as expressed in market prices of the devices, and costs of all clinical services and administrative activities. Calculation of this contribution allows us to assess the impact of these CTs regarding their provision for care, the avoidance of costs by payers, and their contribution to clinical research.

To our knowledge there is no study available to demonstrate the full economic contribution of medical device CTs for a province or country incorporating both funded clinical services and medical devices.

1.9 Tables

Table 1-1: Medical Device Classification

Categorization	Examples
Technologic • conventional • advanced	• examination gloves • cardiac defibrillators
Area of usage (departmental)	• orthopedic • surgical laparoscopic
Degree of invasiveness • invasive • minimally invasive • non-invasive	• maxillofacial implants • coronary stent • stethoscope
Connection-level and integration way with the body • Implantable • injectable drug delivery system • centrally inserted external use • extracorporeal usage • external use • wearable	• cochlear implants • self-Injected drug delivery • cryoablation catheter • extracorporeal circulation system • dressing for severe burns • smartwatches for glucose monitoring
The number of uses • single-use, reprocessible • single-use, non- reprocessible • multiple uses	• electrophysiological catheters • stents • endoscopes
The number of patients • per person use • more than one patient • public use	• artificial pulmonary valve • noninvasive nerve stimulator • magnetic resonance imaging
The purpose • screening • diagnosis • prevention • treatment • monitoring • rehabilitation	• mammography device • positron emission tomography • bioabsorbable cardiac matrix • heart valves • blood pressure monitoring sensors • textile-based robotic devices designed to assist people with mobility impairments

Table 1-2: FDA Medical Device Classification and Regulation

Category	Level of risk to the patient	Examples	Type of review before device be marketed
Class I	Low	adhesive bandage examination gloves sunglasses	need to register Premarket Notification 510 (k), unless exempt
Class II	Moderate	powered wheelchair surgical mask infusion pumps	Premarket Notification 510 (k), unless exempt IDE possible
Class III	High	heart valves breast implants implantable neuromuscular stimulator	must submit PMA IDE probable Premarket Notification 510 (k)

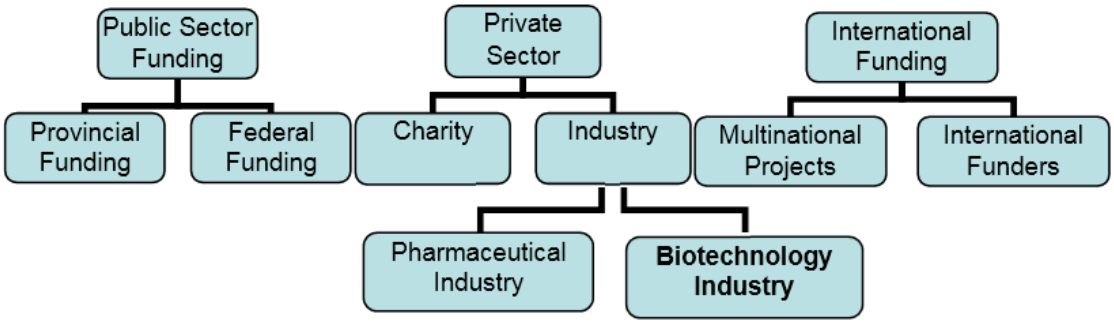
Source: FDA, Overview of Medical Device Regulation, General and Special Controls

Table 1-3: Health Canada Medical Device Classification and Regulation

Category	Level of risk to the patient	Examples	Quality system requirement (CAN/CSA-ISO 13485:2003)	License requirements
Class I	Low	urine drainage bag examination gloves sponge gauze	No	establishment license
Class II	Moderate	vasectomy kit nephrostomy catheter flexible sigmoidoscope	Yes	product license
Class III	High	doppler ultrasound ventilator biliary Stent	Yes	product license
Class IV	Very High	cardiovascular stent pulmonary artery band pacemaker	Yes	product license

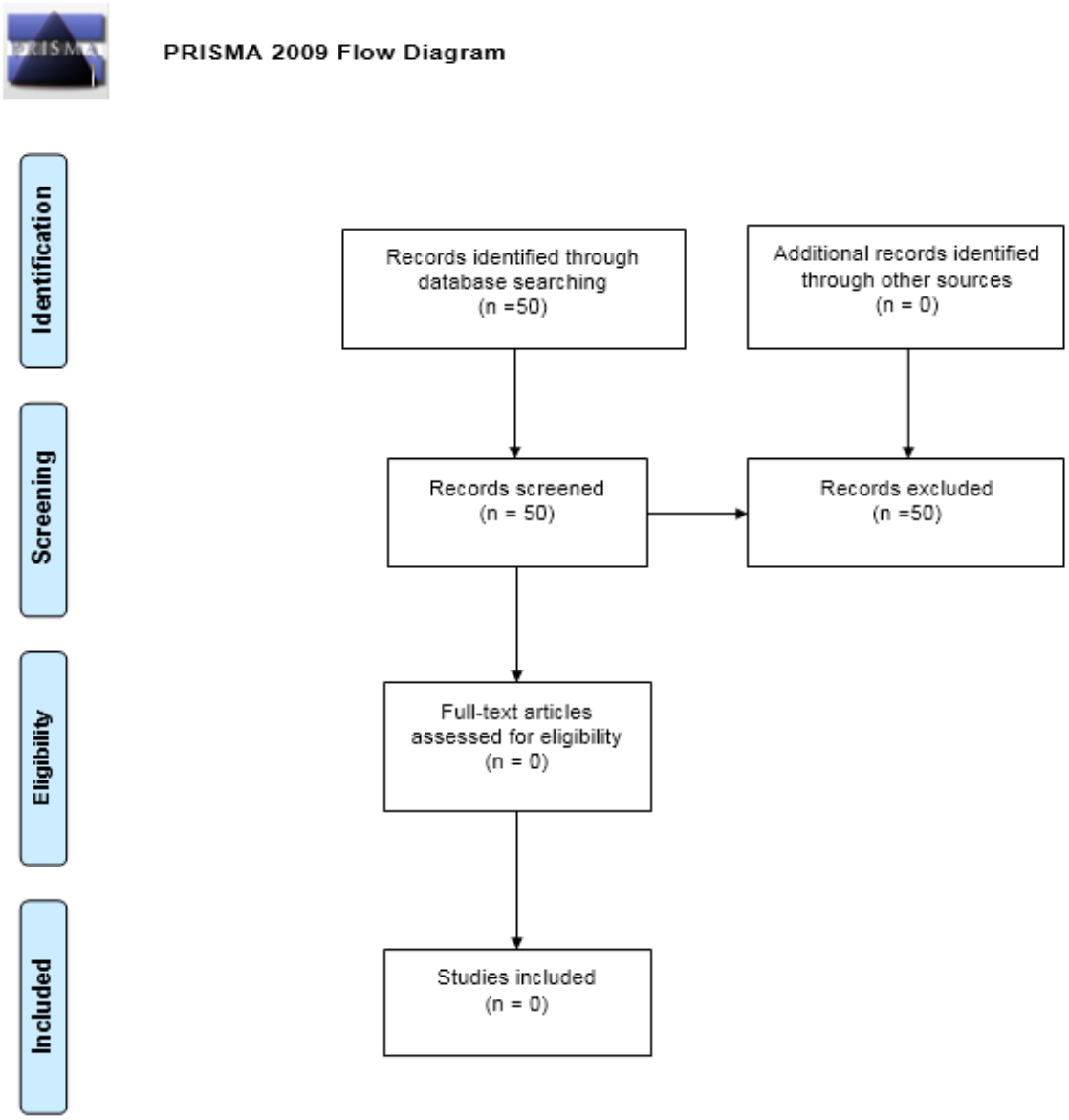
1.10 Figures

Figure 1-1: Research Funding Bodies in Canada



Source: Nason E: Health and Medical Research in Canada – Observatory on Health Research Systems. 2008, Santa Monica, CA: RAND Corporation (33)

Figure 1-2: PRISMA flowchart



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.* PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Chapter 2: METHODS

2.1 Environment

The healthcare system in Alberta has a single province-wide, fully-integrated, institutional service provided by Alberta Health Services (AHS) (35). Alberta health authorities and hospitals provide 70% of medical device funding. Some devices are purchased or funded through a provincial health ministry-led specialty program. The Alberta Aids to Daily Living Program provides financial assistance for the purchase of medical equipment for people with long-term physical disability, chronic or terminal illness (24). Medical devices are funded by a variety of public and private programs, thus the replacement cost for medical devices in clinical trials will impact both public and private funders (24).

The study sample data was obtained from the Northern Alberta Clinical Trials and Research Center (NACTRC) - a joint venture of the University of Alberta and AHS. NACTRC is responsible to develop a comprehensive clinical research administration, operation and support framework localized in Edmonton, including Cross Cancer Institute, Glenrose Rehabilitation Hospital, Kaye Edmonton Clinic, Mazankowski Alberta Health Institute, Royal Alexandra Hospital, Stollery Children`s Hospital and University of Alberta Hospital. NACTRC does not have any data from Covenant Health Hospitals. NACTRC is also responsible for negotiating clinical trial agreements and research approvals in Northern Alberta (36). NACTRC data describing the CTs, including protocols and budgets, are maintained in a central database. Clinical services budgets and overheads, which go into the contracts, are set by AHS-Finance and reflect actual costs. Research teams submit the invoices to the trial sponsors (industry). Payments are received and deposited in AHS accounts. Investigators and their teams manage expenses and payment tracking and make

reimbursement (e.g., salary) submissions to AHS-Finance for team activities (research staff are employees of AHS) (37).

2.2 Variables of Interest

To describe the industry contribution, we included the following variables in our analysis: the market value of the medical devices used in the trials; revenues billed to the industry for clinical and other services; and administrative expenses for each trial. For those trials we included all covered costs in our estimates. The average value per CT formed the basis on which we estimated the value of all CTs in the province.

2.3 Trial Sample

Our target sample included all industry-sponsored medical device CTs that were processed through NACTRC and were initiated between January, 2012 and January, 2016. The ending date we chose for our analysis is January 30, 2018. The start date was chosen to allow for sufficient time for the trials to end. We obtained the trial budgets from NACTRC, and the number of patients enrolled in each trial from the University of Alberta Research Ethics Board. We contacted the research ethics board to obtain on-going (not completed) trials and the number of patients enrolled in the study with an end date of January 2018. For the number of CTs in the entire province, we used the total number of industry-sponsored medical device CTs which were enrolled between January, 2012 and January, 2016 as per the website *ClinicalTrials.gov* (5).

2.4 Cost of Clinical Trials

Estimating Industry Billings for Clinical Services

We used trial budgets to measure billings for each trial. In the absence of an industry sponsored

trial, the services related to these billings would have been paid for by the healthcare system as part of the standard of care. We measured service costs according to trial protocols and categorized billed services into three major groups: 1) management billings (including start-up costs, storage of study device, document preparation and archival costs), 2) research ethics board fees, and 3) patient service billings (laboratory tests and imaging, procedures, consultations, treatments of adverse events). Billings for individual trials were summed to yield the total billings of the study sample. Budgeted rates included direct service costs plus estimated overheads.

Medical Device Pricing

We used the CT protocols from the website *ClinicalTrials.gov* (8) to identify the devices used in the study. We developed a hierarchical method to identify the market price of each device (38). First, we examined the clinical trial budgets to see if the device price was provided and then made a request to the manufacturer. If a price was not found in the budget document and the manufacturer did not provide the list price, we used the U.S. price of the device based on a reported paid price, provided by Innovative Health, Scottsdale, Arizona (39). If a price was not found in Innovative Health's database, we obtained data from the published literature (using cost-effectiveness studies and health technology assessment reports). Finally, if none of the above data was available, only the trial budget information—and not the device cost—was considered for the analysis. All prices were converted to Canadian dollars (C$) using purchasing power parity (PPP) measures obtained from Organisation for Economic Co-operation and Development (OECD) data (40), and values were presented in 2018 C$. The device cost for placebo treatments was set to nil. The source of pricing for CT devices is presented in Table 2-1.

All monetary values were presented in 2018 Canadian dollars. We did not include inflation

adjustments for device prices, because of the way the medical device market works. It is expected that the device price would decrease or stay stable considering rapid technological development and the devices' short lifetimes (41). For the trial budgets we applied the inflation rates using the all-item Consumer Price Index for Alberta (42).

Estimating the Province-Wide Contribution of Industry-Sponsored Clinical Trials

We multiplied the estimated average value per by the number of industry-sponsored medical device CTs (49 trials) that were initiated between January, 2012 and January, 2016 to have the total value of all industry-sponsored device CTs in the province. To do this, we searched for industry-sponsored medical device CTs initiated during the time period in Alberta. We found 71 CTs according to clinicaltrials.gov (8). We excluded 22 which were not using medical devices; these comprised a clinical tool development project, a disease-specific patient-reported outcome instrument study and a rehabilitation assessment program.

2.5 Sensitivity Analyses of Device Prices

We conducted a sensitivity analysis to estimate the price range effects on the total device costs of CTs. We calculated the minimum and maximum device price ranges in percentages for four medical devices and applied this to all medical device prices.

2.6 Statistical Analyses

Total economic values were calculated for trials in four major categories (management billings, ethics review fees, patient service billings, and device costs). Service billings were calculated by arm—experimental and control arms. There was a large difference between trials regarding the

type of disease, clinical procedure, laboratory test, and type of device used. Therefore, we did not report variations in economic values as these would be less informative.

We also calculated the length of each CT in months from its start date to its end date or to our study end date of January 2018, whichever came first, and reported the CT lengths in months (±standard deviation). All analyses were performed using Microsoft Excel version 2016 (Microsoft Corp., Redmond, Washington).

2.7 Tables

Table 2-1: Source of CT device pricing (n=18)

Source of the device price	Number of trials
Clinical Trial Budget (actual price)	1
Reprocessing Company and Institutions (actual price)	9
Manufacturer (list price)	2
Published Literature (list price)	6

Chapter 3: RESULTS

We obtained the list of 54 CTs from NACTRC, and 31 (57%) of them were industry sponsored, leaving out 23 CTs which were not industry sponsored. We also excluded further 3 trials which did not use medical devices but were specifically designed to develop a clinical tool, evaluate a disease-specific patient-reported outcome instrument or a rehabilitation assessment program. In total, there were 28 industry-sponsored medical device trials initiated between January, 2012 and January, 2016 in the NACTRC database. Budget information was not available for 3 of 28 included studies, so we obtained complete data on 25 medical device trials. We excluded two medical device trials because of zero enrollment (Figure 3-1).

Of the twenty-three medical device trials remaining for analysis, the most common device group was cardiologic with twelve (52%) devices. Twenty of the devices (87%) were classified as minimally invasive by the manufacturer. Twelve (52%) of the devices were implantable and eighteen (78%) of all devices were single use. Except for one preventative device, all other devices in our study were for treatment (96%).

Nine of the included twenty-three studies (39%) were randomized controlled trials (RCTs), while thirteen of them (57%) were single-arm studies. One cohort study had four groups. Twelve of the clinical trials were closed, one was terminated and ten of them were still active in January 2018. The mean duration for the medical device trials was 44.6 months (±17.5 months, min 6 months, max 71 months) up to the end of our study in January, 2018. The number of participants in the experimental and control groups are shown in Table 3-1.

We could not find the device price information for five CTs, and only the trials' clinical and administrative costs were included in these instances. One of these CTs was terminated before

market entry and for the others, the devices were not on the market. We used the actual price of the device as our first choice, and this covered 10/18 (56%) of CTs. For less than half of the trials, we used the list price (Figure 3-2). We derived the device price information from different locations—nine from the U.S., four from Canada, four from the U.K. and one from Australia (39, 43-50).

3.1 Economic Value of Clinical Services in Standard Care as Part of the Clinical Trials and Economic Cost of Devices as Part of the Clinical Trials

The standard of care patient service billings accounted for C$3.8 million whereas C$1 million were related to management fees and ethics review board costs (Table 3-1). Medical device companies provided the trial devices for free in 20 (87%) clinical trials; institutions paid for the study device in the remaining three. The total device contribution for the included trials was C$4.7 million (Table 3-1). About 12% of the trial budgets were allocated to the administrative activities of the trials, and 88% of the value of trials went for patient services and devices in trials. Devices accounted for 55% of the total economic contribution of the device CTs (Figure 3-3).

The total values for the included medical device CTs were C$8.5 million (Table 3-1). On a per-patient enrolled basis the contribution to the health care system was C$19,427 for medical device CTs. On a per-trial basis, the industrial contribution to the healthcare system was C$368,261.

3.2 An Extrapolation to Province-Wide Costs of Clinical Trials

We multiplied the estimated average value (C$368,261) per trial by the number of industry-sponsored medical device CTs (49 trials). Doing this, we extrapolated NACTRC initiated, industry-sponsored medical device clinical trial costs to the entire province of Alberta between January, 2012 and January, 2016. The value to the healthcare system of industry-sponsored device

CTs in the entire province of Alberta was C$18 million. This value approximates the value of CTs initiated over the specified time period in the province of Alberta.

3.3 Sensitivity Analyses

In the sensitivity analysis we had the minimum and maximum price information for only four of the devices (22%). We calculated the minimum and maximum price range for these four devices. The device price ranged from %82 to 137%. We assumed that minimum and maximum prices for all included medical devices would be in the same range. Minimum device price usage for devices led to a reduction of C$847,559 in device costs, and resulted in a reduction of the revenue per trial for medical device CTs from C$368,261 to C$331,410. Accordingly, the province-wide contribution of industry-sponsored device CTs would fall from C$18 million to C$16.2 million. Instead, using maximum device prices for four devices would lead to an increase to C$21.8 million in CTs (Table 3-2).

3.4 Figures

Figure 3-1: Industry- sponsored medical device CT selection from the NACTRC database

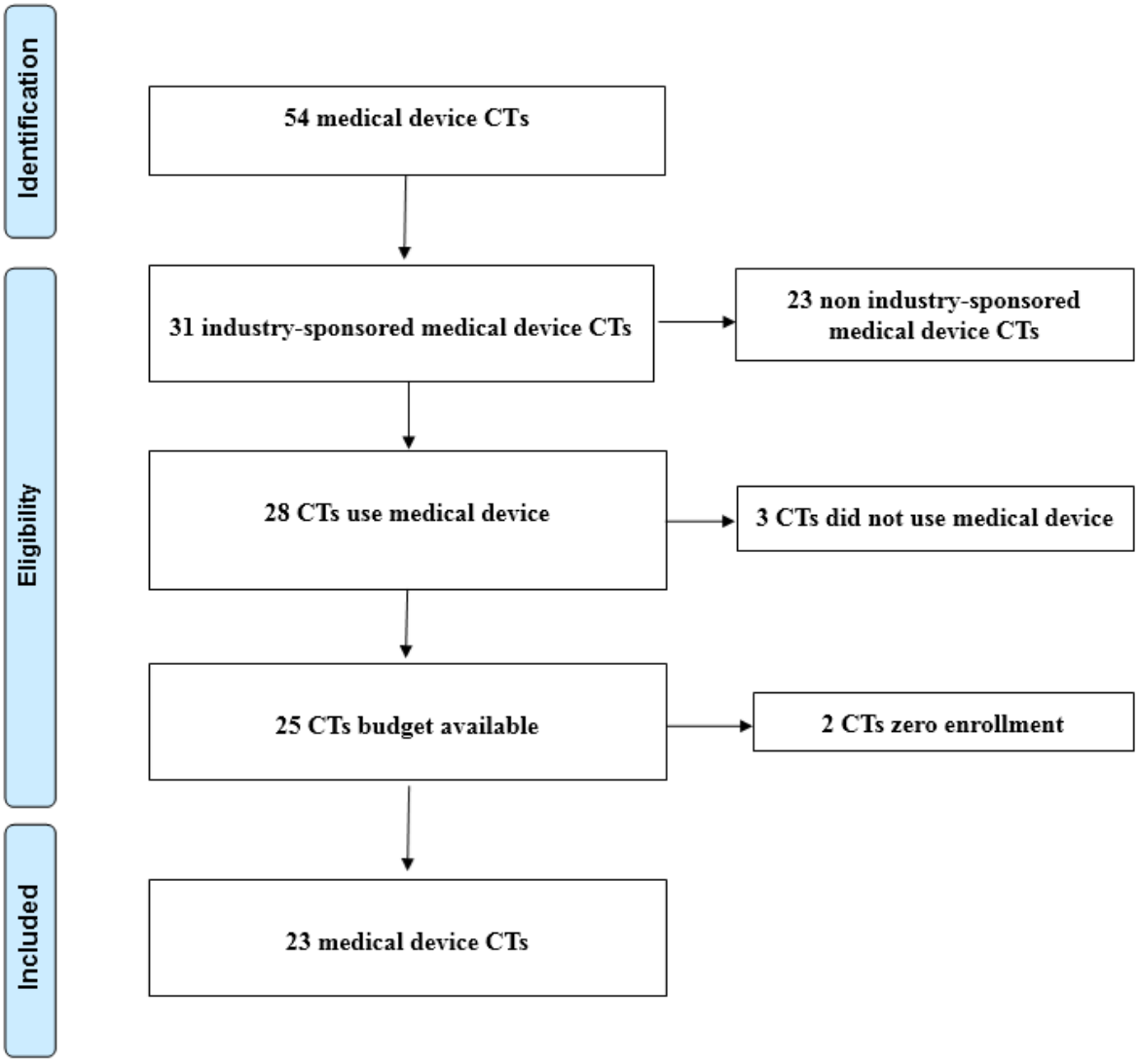


Figure 3-2: Medical Device Market Price Identification

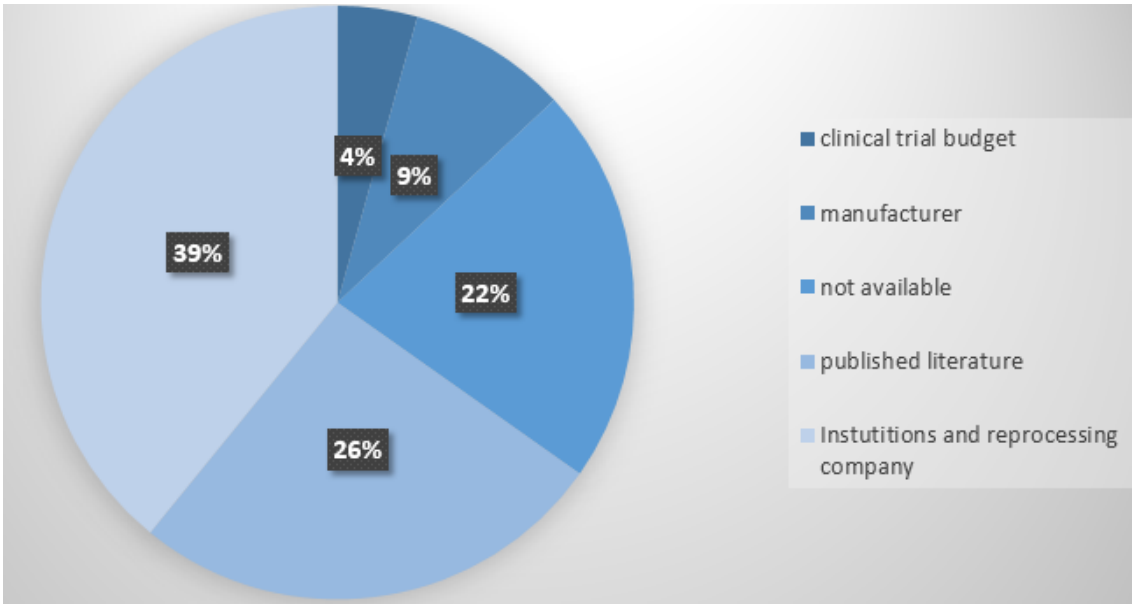
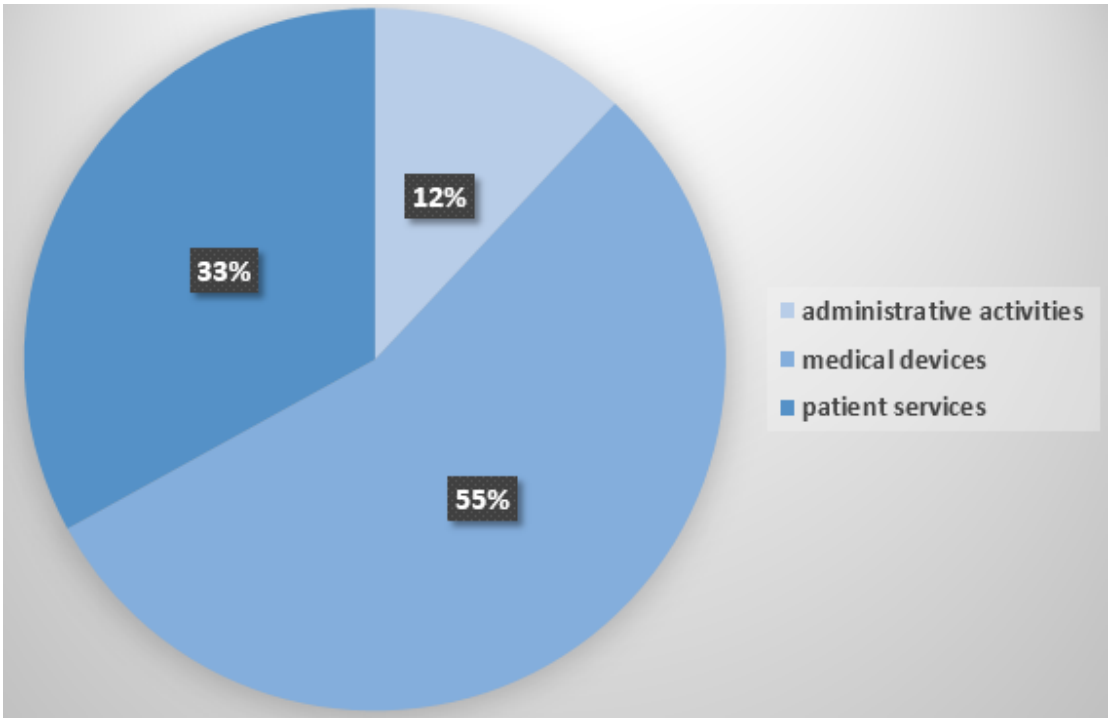


Figure 3-3: Components of Trial Budget



3.5 Tables

Table 3-1: Total cost in each cost category of the medical device clinical trials (n=23)

Variable	Number of enrollees	Average value per trial	Total value (2018 CAN$)
Medical Devices		$261,592	$4,708,661
Management billings		$36,552	$840,695
Ethics review fees		$7,546	$173,549
Clinical services (Experimental arm)	353	$91,671	$2,108,433
Clinical services (Control arm)	83	$51,855	$518,552
Trial budgets presented as a total			$120,104
Overall for all enrollees	436		
Without medical device cost			$3,761,333
With medical device cost			$8,469,994
Per trial base industry contribution			$368,261
Province-wide industry contribution			$18,044,789

Table 3-2: Sensitivity analysis of the results

Variable	Minimum	Average	Maximum
Medical device cost	$3,861,102	$4,708,661	$6,450,866
Total clinical trial cost	$7,622,435	$8,469,994	$10,212,199
Per trial base industry contribution	$331,410	$368,261	$444,009
Province wide industry contribution	$16,239,090	$18,044,789	$21,756,441

*using four medical device minimum and maximum price information (2018 C$)

Chapter 4: DISCUSSION

We estimated the economic contribution of industry-sponsored medical device CTs to the Alberta healthcare system. Overall the average revenue per medical device CT was C$368,261. In total, industry-sponsored medical device CTs were estimated to contribute $18 million over the four-year study period. About 12% of the trial budgets were allocated to the administrative activities of the trials, and 88% of the value of trials went for patient services and devices in trials. Medical devices accounted for 55 per cent of total CT costs.

These results are indicators of the cost of services provided to patients, which (primarily) the Government of Alberta or private payers would have had to pay for in the absence of the clinical trials. In general, the public payer would have paid for all included devices in our analysis except for one dental device. This device could be paid in either way, public or private. This amount is also a reflection of what a government research sponsor would have to pay to generate clinical research. Although basic research gets the most attention in the device area, clinical research for medical devices has been growing in importance.

While we only considered the industry contribution to the health care system, medical device companies incur other research-related expenses that we did not include—such as company administrative costs, internal monitoring costs, the cost of preparing and submitting clinical trial applications and amendments to the regulatory agencies, etc. Although these items are not part of the economic contribution to patient care, they are part of the contribution to the research and development process.

The device companies' expenses vary depending on the companies' structures. The medical device industry consists of a few large, well-known companies and many small companies. Small

companies usually play a role in the initial discovery and development stages of the new devices. Meanwhile, the large medical device companies lead most of the industry-sponsored research (51). Although companies perform medical device clinical studies, there are no explicit standards exist for the sample size, follow-up period or subgroup analyses for medical device CTs. Fewer enrollment rates for medical device CTs compare to the drug trials, makes it difficult to inform the clinicians and public as to whether the new medical device can cause adverse events. To collect more reliable data for adverse events and clinical effectiveness, the health authorities could increase the CTs numbers in their health region and they could also encourage their research institutes to follow more rigorous CT methodology.

In 2017, the revenues of the top 10 largest medical device companies ranged from $28.8 billion to $10.1 billion globally (52), and these companies spent almost 10 percent of their revenues on research (53). The companies that produce advanced products, in general, spend more on the research and development than the others (54). Even though we know what the industry spends on research, it is important to understand the contribution of these expenses to the regional economy, clinical research and development.

There is no current data on the full economic value of *medical device* CTs. The only study (37) that we found captures the full economic contribution of industry-sponsored *pharmaceutical* CTs including clinical services as well as drugs to Alberta's healthcare system. Our findings can be compared with pharmaceutical CTs. On a per-trial basis, the industrial contribution to the healthcare system was C$368,261 for medical device CTs compared to $467,303 and $630,243 per non-cancer and cancer drug CTs, respectively (37).

Even though the province-wide contribution of medical device CTs was C$18 million in our study, the economic contribution of CTs might be underestimated because of the missing price information for five (22%) medical devices.

There are several reasons that make it difficult to evaluate the contribution of device CTs. After the new device gets approval, the manufacturer can charge high prices, due to the monopoly and the lack of price regulation mechanisms for medical devices. Manufacturers' list prices are often the starting point for negotiations, and they are not always representative of the actual price. It is difficult to get actual price information due to the commercial agreements relating to the disclosure of the products prices. The price of a new device may vary significantly from one hospital to another, even between different purchasers for the same product. There is very little public information about prices for new medical devices; to the extent that the maximum price for some medical devices is often more than twice as much as the minimum prices (55).

Growing healthcare costs leads to an increasing demand for evidence-informed resource allocation. Canada spent C$242 billion on health care in 2017 (56). Even though it is not well tracked, it is estimated that 3% of this annual budget is spent on medical devices (24). It is essential to conduct high-quality economic evaluations to provide robust information from economic impacts of the new medical devices to policymakers. Economic evaluation, as a data-driven process, needs to be supported by reliable data sources. Medical device prices are important variables in CT budgets and essential components of economic evaluations. However, documenting unit prices for medical devices has some challenges (38).

The prices charged by manufacturers of medical devices are usually confidential, and can vary widely. Getting actual price information is difficult. Even if we had list prices, manufacturers' list

prices are not always representative of the actual price paid by different end users. They are often the starting point for negotiations. In the absence of market prices, economic evaluations are usually conducted using proxy prices or list prices (if available) for the devices.

We calculated the minimum and maximum price range, which varied from 82% to 137%, and minimum device price usage for devices led to a reduction of the province-wide contribution of industry-sponsored trials form C$18 million to C$16.2 million. Instead, using maximum device prices would lead to increase to C$21.8 million in CTs. In addition to the price variations effects on the industry-contribution to the CTs, price variations also have a considerable effect on the cost-effectiveness ratios, since device costs became important components of total procedure cost.

Decision makers use economic evaluations for reimbursement decisions, and cost-effectiveness ratios became as a common-metric tool to access the implications for health-care technologies. Considering device price variations, we would expect significant changes in cost-effectiveness ratios which is one of the key determinant tools for reimbursement decisions.

Before a product is launched, the policymaker or manufacturer may want an advanced study, yet there is no publicly available pricing information for conducting the economic evaluation. A literature review aimed at identifying the medical device prices have shown that, only less than half of the studies in published Canadian economic evaluations used the actual transaction price (57). In our evaluation we found the actual price information only for ten medical devices, and we used the list prices for eight devices in our analysis.

Even though our study provides information on the economic contribution of industry-sponsored medical device CTs in the province of Alberta, it has some limitations. First, we could not get device price information to estimate the contributions of five medical device trials. Therefore, the

study results should be interpreted with caution. One of these CTs was terminated and for the other four, the devices were not on the market. The device price is usually quite high when the device first comes to the market; so, the total contribution of industry-sponsored device CTs could be substantially higher.

Second, we used 2018 actual price information provided by the medical device reprocessing company (Innovative Health) and institutions for nine of the devices included in this analysis. Considering the CTs included in this analysis conducted between January, 2012 and January, 2016, the prices for a particular model of the medical device could rise and fall over time. Prices for the device models in the CTs can decline over time if the improved versions of the product become available in the market (58), so we could underestimate the industry contribution for medical devices, taking into account the 2018 prices of the current models of the new devices.

Third, we also used prices for the U.S., the U.K. and Australia where we could not find Canadian prices. The medical device prices differ between these countries. The prices are higher in the U.S. than Canada, so this could imply a substantial reduction in the total contribution of industry-sponsored device CTs in Canada. However, it should be noted that our study included experimental devices that were not on the market in Canada. Therefore, their prices at launch in Canada would be expected to be close to the prices in the U.S.

Finally, considering that NACTRC does not include data from some small institutions in the Northern Alberta, like the clinical trials conducted at the Covenant Health Hospitals, and the Southern Alberta, we obtained the provincial volume of trials data from the website, *ClinicalTrials.gov* (8). Even though Health Canada Clinical Trials Database is providing to the public a list of specific information relating to clinical trials, the database has information only

about pharmaceutical and biological drug CTs (59). The information on conducting medical device CTs could not be obtained even from one Canadian source. We could have also missed some unregistered trials that were started between January, 2012 and January, 2016 with the *Clinicaltrials.gov* (8), because as stated by the 21st Century Cures Act; "Trial sponsors may request posting of trial data on the ClinicalTrials.gov website prior to final clearance or approval of their devices", but not at the beginning of the trial (60).

Chapter 5: CONCLUSION

Having well-organized research centers brings benefits to the regions, not only with their impact on the scientific knowledge and provision of high-quality medical care, but also with their contribution to both public and private funding stream of healthcare.

This thesis is the first to provide a comprehensive assessment of economic characteristics of industry-sponsored medical device clinical trials in a population-wide database in Alberta, Canada. Our estimates indicate that, the industry's contribution to the value of devices and clinical services in medical device CTs amounted to C$18 million, which has been ignored in the past. To adequately evaluate this contribution, a reliable measure of the cost of medical device trials is necessary, and the value presented in this study can inform the creation of new financial and regulatory public policies and encourage regions to strengthen their market provision.

Our results showed a considerable difference between the economic contribution of industry-sponsored clinical trials using the minimum and maximum device prices. It is important to report device prices in economic evaluations, since it may have a significant impact on cost-effectiveness estimates which is an important tool for decision makers.

The current study focuses on the data from one province — the province of Alberta. Future research could extend the soliciting new data from other provinces even nationwide. Regions can strengthen their market position if relevant authorities, policymakers, and investigational site management teams recognize this contribution and support the conducting of clinical trials.

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APPENDIX

Appendix 1:

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 exp "Equipment and Supplies"/ or medical device*.mp. (1349777)

2 exp Clinical Trials as Topic/ or clinical trial*.mp. (1015169)

3 (economy adj2 (regional or provincial or federal or national)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (676)

4 (economic adj2 (contribution* or impact* or value*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (12288)

5 3 or 4 (12937)

6 1 and 2 and 5 (50)

7 exp "Equipment and Supplies"/ or medical device*.mp. (1349777)

8 exp Clinical Trials as Topic/ or clinical trial*.mp. (1015169)

9 (economy adj2 (regional or provincial or federal or national)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (676)

10 (economic adj2 (contribution* or impact* or value*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (12288)

11 9 or 10 (12937)

12 7 and 8 and 11 (50)

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