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Qualitative Evaluation of the Canadian Fabry Disease Initiative Using Key Informant Interviews

by

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ABSTRACT

The objectives of this study were to evaluate the Canadian Fabry Disease Initiative (CFDI) using input from key informants. A qualitative strategy composed of interview transcripts, a holistic-inductive design and content analysis was used. Within group analysis suggested: (1) patients are concerned about the restrictions on access to therapy; (2) CFDI investigators believe the database and monitoring are essential components to treating rare diseases, but the CFDI is not the ideal model; (3) Provincial representatives believe research should not be a foundation for drug access; and (4) pharmaceutical representatives perceived the CFDI as a poorly designed answer to a reimbursement problem. Between group analysis revealed that the CFDI as an important initiative in Canada. However, it is not the solution to many of the issues related to orphan drug reimbursement. Overall, no group was completely satisfied with the CFDI therefore it should be redesigned to better accommodate each group's needs.

LIST OF ABBREVIATIONS AND SYMBOLS USED

CADTH- Canadian Agency for Drug and Technology in Health

CDD- Canadian Drugs Directorate

CDR- Common Drug Review

CEDAC- Canadian Drug Expert Advisory Committee

CFDI- Canadian Fabry Disease Initiative

CIHR- Canadian Institutes of Health Research

CORD- Canadian Organization for Rare Diseases

EDRD- Expensive Drugs for Rare Diseases

EDRP- Emergency Drug Release Program

EMEA- European Agency for Evaluation of Medicinal Products

ERT- Enzyme Replacement Therapy

FDA- Food and Drug Administration

FPTTF- Federal, Provincial and Territorial Task Force

FRSQ- Fonds de la recherché en santé du Québec (FRSQ)

HCC- Health Council of Canada

ISOC- Independent Scientific Oversight Committee

NPS- National Pharmaceuticals Strategy

ODA- Orphan Drug Act

ODP- Orphan Drug Policy

PMPRB- Patented Medicine Prices Review Board

R& D- Research and Development

SAP- Special Access Program

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CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION

This paper is designed to first introduce the reader to rare diseases, expensive drugs for rare diseases and the Canadian history of policies and recommendations that were developed to help Canadians with rare diseases better afford and access their treatments. With this background provided, the reader will then be introduced to the Canadian Fabry Disease Initiative (CFDI), the most recent model designed to provide enzyme replacement therapy to Canadians with Fabry disease. The paper then introduces the use of qualitative social program evaluation in health research and how it will be applied to the present study to evaluate the CFDI using key informant interviews. Finally, the results of the content analysis will be presented and discussed. All terms discussed in the introduction will be addressed in greater detail in the body of the paper.

It was the purpose of this research project to qualitatively evaluate the CFDI from variety of perspectives using key informant interviews. An evaluation will help identify areas of strengths and weaknesses help elicit issues arising from each group's perspectives, and determine the potential of the CFDI to be the solution to a national orphan drug policy in Canada. Ultimately, the evaluation will provide information about the CFDI's progress in reaching its own outcome goals, and present recommendations for improvement. This information can be very valuable for future development of the CFDI and other similar initiatives.

Based on international standards, to be classified as 'rare,' or 'orphan,' a disease must affect no more than 1 in 20,000 individuals. In Canada, there are over 6,000 orphan diseases that affect over 3 million citizens, many of whom do not have access to treatments through current Canadian drug policy. Canada has yet to develop a national orphan drug policy (ODP) that would provide equitable access to expensive drugs for rare diseases (EDRD) across Canada and facilitate research and development of such drugs.

Currently, Health Canada assesses drugs for safety, efficacy and quality. If drugs comply with Food and Drug regulations, they are served a Notice of Compliance and can be legally distributed in Canada. Drug expenses in Canada can be either fully or partially covered by private insurance or provincial/territorial drug benefit programs. Certain groups, such as Royal Canadian Mounted Police, and military members are covered by federal drug benefit programs. For a variety of reasons many Canadians remain without a drug insurance plan. The method of assessing drugs for reimbursement recommendations in Canada is headed by the Canadian Agency for Drug and Technology in Health (CADTH). The Common Drug Review (CDR), housed within CADTH, provides recommendations to all provinces (excluding Quebec) regarding which drugs should be added to provincial drug formularies. Overseen by the Canadian Expert Drug Advisory Committee (CEDAC), the CDR assesses drugs for clinical and cost-effectiveness based on clinical research outcomes provided by the manufacturer and available literature. Provinces decide independently whether or not to cover the drug. If covered, those eligible for the benefits are reimbursed for the drug. Provinces can also provide restricted coverage

of a drug for certain patients and patient populations. For example, an advocacy group or person may lobby for access to a drug that was not listed on the formulary.

Due to the nature of rare diseases, there are fewer trials conducted to assess clinical effectiveness of orphan drugs, and these drugs are much more expensive in comparison to common prescription drugs. Furthermore, due to these inherent characteristics of orphan drugs, few have been recommended for reimbursement by the CDR, and hence these pharmaceuticals are not funded by provincial/territorial health-care formularies.

Both the Romanow Commission (2002) and Kirby (2002) reports included recommendations for the development of a catastrophic drug coverage policy that would provide funding for treatment of individuals in life-threatening situations. In 2004, the provincial premiers and the Prime Minister proposed a 10-year plan to strengthen health care in Canada. This proposal included a National Pharmaceuticals Strategy (NPS). The NPS was intended to implement national solutions to rising concerns about the safety and affordability of prescription drugs in Canada. Included in the initiative were strategies to deal with catastrophic drug coverage (catastrophic refers to the financial impact the cost of the drug has on individuals), a national drug formulary, accelerating access to new drugs, and other actions to improve access and costs of drugs in Canada. In 2006, the plan was updated and the NPS was further developed to include strategies to deal with expensive drugs for rare diseases. The NPS report also reaffirmed the Canadian Health Accord statement that no Canadian would suffer undue financial hardship due to the cost of needed therapies. In the 2006 report, the NPS further developed its recommendations and strategies but there has

been no progress in implementing any of the initiatives described, or publishing any progress reports.

Several independent lobbyist groups, such as the Canadian Organization for Rare Disorders (CORD) and BIOTECanada have recommended that Canada adopt a national approach using international ODP principles such as industry tax incentives, market exclusivity, and expedited reviews. However, none of these suggestions have been acted upon on a national basis. Given that Canada lacks all of these factors along with the inability of the CDR to approve expensive drugs for rare disease it is understandable that pharmaceutical companies developing these drugs may be hesitant to apply to the CDR for recommendation of a drug.

The Canadian Fabry Disease Initiative (CFDI) is a national study designed to learn more about two treatments for Fabry disease. This rare disease is a genetic disorder that affects many parts of the body; it will be described in further detail below. Fabrazyme® and Replagal®, two drugs that treat Fabry disease but cost upwards of $300,000 a year per patient, were approved for use by Health Canada, but not recommended for reimbursement by the CDR. The CFDI is designed as a research study to assess the effectiveness of two treatment options for Fabry disease. It has five research sites across Canada with leading Fabry disease-treating physicians and a research team at each site. It was funded through a three-year cost sharing arrangement between treatment providers and the federal and provincial governments. The funding arrangement was originally scheduled to terminate October 1, 2009; however, several provinces (Nova Scotia, Ontario, Alberta, and B.C.), without aid from the federal government, have agreed to continue funding beyond this point (Silverside, 2009). The long-term future of the program itself remains unclear. This

research initiative provides a unique opportunity for robust research that can contribute to a future CDR evaluation on these two treatments (CIHR, 2008). In the future, such initiatives may provide a means for other patients who suffer from rare diseases to gain access to needed therapies.

The purpose of this study was to use interviews with key informants to qualitatively evaluate the CFDI, using a content analysis approach as recommended by Patton (2002) and Erlandson, Harris, Skipper & Allen (1993). Key informants included CFDI investigators (physicians, nurses and coordinators), patients, patient representatives, pharmaceutical representatives and provincial government representatives. Participants were asked various questions regarding their experiences and opinions of the CFDI as a clinical study, as a method of drug access and as a prototype program for improving patient access to expensive drugs for rare diseases using a national platform. The primary objective of the study was to gain a holistic portrait of the CFDI that would be used to help determine whether it is viewed as a preferable model to improve access to other expensive drugs for rare diseases, and, if not, what would be preferred instead. Additional goals included identifying areas of strength and weakness, and gaining information on a variety of CFDI experiences.

This paper is divided into six chapters: introduction, literature review, methods, results, discussion and conclusion.

Chapter two, literature review, will provide background information on rare diseases (particularly Fabry disease), expensive drugs for rare diseases and the history of Canadian initiatives to improve health care in the area of drug coverage, such as the Romanow Report and the National Pharmaceuticals Strategy. This chapter will also cover the process of drug reimbursement in Canada, the Common Drug Review,

and will review international policies regarding EDRD. Chapter two will end with a description of the CFDI and a discussion of the significance of this research.

Chapter three, methods, will describe the study participants, objectives and design. Here, a description of the use and importance of qualitative evaluation methods in program evaluation, and then the use of content analysis for data analysis will be provided. This will put the research study methods in perspective for the reader.

Chapter four, results, will provide the results of the study, including within and between case analysis results, and a variety of quotations from all key informant groups

Chapter five, discussion, will examine the results with reference to the research questions.

Chapter seven, conclusions, will look at not only at conclusions but also limitations and future possibilities.

CHAPTER 2: LITERATURE REVIEW

2.1 Definitions of Rare Diseases

Diseases which are classified as a rare, or "orphan," by definition affect a small proportion of the population. In Canada, there is no official designation for what qualifies a disease as 'rare.' The rare disease patient advocacy group, the Canadian Organization for Rare Diseases (CORD, 2007) defines an orphan disease as one that affects approximately one in 20,000 people, meaning a maximum of 1,750 people in Canada for any one particular disease (estimated from the 2006 population from Statistics Canada [2008]. The World Health Organization (WHO) defines it as a disease that affects less than a thousand per million. Using WHO's international standards, it is estimated that for a disease to be classified as rare it would affect no more than 35,000 individuals in Canada.

When viewed as a whole group, rare disease sufferers constitute a large sample of the population. There are over 6,000 discovered rare diseases which cumulatively affect over 3 million (about 10%) Canadians (CORD, 2007). Internationally, rare diseases affect anywhere from six to 10% of the entire population, that is, about 30 million Europeans or 25 million Americans (Zurnisky, Reeve, & Elliot, 2007). Approximately one in 10 individuals will be born with a rare disease, many of which have no known treatment. Cumulatively, rare diseases have a significant impact on the health-care system, the individual and their families (NORD, 2007) as many orphan diseases result in progressive deterioration of health and lifestyle, leading to an increasing need of homecare and continuing care.

Rare diseases present several problems for both the patient and the health-care system. Due to the small populations and often heterogeneous symptoms, rare diseases are difficult to diagnose for general physicians, meaning many patients go untreated for their disease. These conditions are also commonly debilitating and disabling, and take a heavy toll on individuals, their family and health-care services (U.S. Department of Health and Human Services, 2007). Onset regularly begins in childhood and continues throughout life. The psychosocial effects of rare diseases are very serious because of the lack of treatment, hope and often random prolonged periods of pain (Eurordis, 2005).

2.2 Fabry disease

Fabry disease is a rare, inherited, genetic condition that affects about 350 Canadians, most of whom live in Nova Scotia. The disease is an X-linked genetic disorder that has progressively deadly costs to the individual due to a deficiency of an enzyme called alpha-galactosidase A (Gibas, Klatt, Johnson et al., 2008). Without this enzyme, glycolipids build up within the cells of affected individuals and over time can cause kidney disease, heart disease, stroke, neuropathic pain, and early mortality. Due to the X-linked nature of the disease, the condition is generally thought to be more prevalent in females but more symptomatic in males. This is because affected females have one mutant and one non-mutant X chromosome, and it is thought that the healthy chromosome offsets the mutant chromosome which can result in females being asymptomatic (Gibas, et al., 2008). However, this assessment has been challenged recently and several researchers now argue that females suffer from a greater disadvantage because the disease may be misdiagnosed (Gibas, et al., 2008).

Without treatment, persons with Fabry disease can develop severe neuropathic pain, kidney disease, heart disease, stroke and/or premature death, often before the age of 60 years old (CIHR, 2008).

2.3 Definition of Orphan Drug (or Expensive Drugs for Rare Diseases [EDRD])

Orphan drugs are defined by the fact that they treat orphan diseases; they are also known as expensive drugs for rare diseases. Research of their effectiveness often is limited because of small sample populations. Research is even more limited in Canada, when compared to research for common drugs. For example, in 2006, pharmaceutical companies spent over $1.2 billion to research drugs in Canada; however only 2% was spent researching all new drugs (Canadian Generic Pharmaceutical Association, 2007). Inclusive in that 2% is a negligible amount of funding for new EDRD. Due to the lack of an official Canadian definition of EDRD or rare disease, the exact figures are unknown. This number is troubling because most orphan diseases are genetically based and require expensive biotechnology equipment for research. In addition, orphan drugs are expensive and are generally not covered by provincial formularies or private health-care insurers (Health Canada, 1997). The majority of orphan drugs are new or "breakthrough" drugs, but there are also older drugs that have not been approved for use, and drugs that were once approved but have since been removed from the list of approved drugs.

2.4 Previous federal and provincial policy initiatives and recommendations

Currently, final decisions regarding reimbursement for Health Canada-approved pharmaceuticals for public drug plans is up to the individual provinces,

which has created unequal access to treatments across Canada. Many previous reports have recommended the federal government contribute to a national drug program that would level the field of drug access. This section reviews the previous recommendations made by federal task forces and royal commissions to improve drug access and affordability in Canada. Although there have been several major reports written such as the Romanow Commission Report, nothing has been done on a national basis to improve access to EDRD. Additionally, individual provinces like Alberta and British Columbia have developed policies regarding expensive drug coverage. These reports and new policies are important to consider and discuss in an evaluation of the CFDI for a comprehensive picture of Canadian history on the subject and comparison reasons.

In 1997, the Canadian Drugs Directorate (CDD) of Health Canada conducted an analysis of Canada's policies and procedures with respect to orphan drugs (Health Canada, 1997). Its subsequent report stated that Canadians had equitable access to orphan drugs through the process of the Emergency Drug Release Program (EDRP). No new policy recommendations were made. This was seen as a major blow by those seeking treatment. The CDD did not even recommend including the term 'orphan drug' as a distinction for these types of treatments, thus ignoring the separate status reserved for them in many other countries. International policies will be reviewed in an upcoming section.

The EDRP handles approximately 50,000 applications annually (Robinson, 1995). The physician-initiated program allows for quick access to drugs that have not been approved by Health Canada but have demonstrated some clinical effectiveness. However, the EDRP does not provide funding for the drugs. This is levied on the

patient, or the private, provincial or federal drug plan depending on the arrangements. Although 50,000 submissions might appear to be a large number, many do not get fully processed because of the amount of paper work, and the reluctance of physicians to follow up on submissions (Robinson, 1995). Physicians are also required to provide feedback on the treatment effects (Gilron, 1993). The process has been called labour-intensive and oppressive (Robinson, 1995). The primary physician also assumes the responsibility for the patients once the treatment has begun. There is a risk/benefit aspect to applying for a drug before it has been approved for safety. A physician must take into consideration several factors such as the patient's condition, his/her response to other treatments, and the available evidence on the requested drug (Gilron, 1993).

The EDRP assumes that physicians are familiar with the rare disease a patient may have and its treatment, which is often not the case (Eurordis, 2005). Very few orphan drugs have been approved through this process (Health Canada, 1997). Lack of coverage for orphan drugs remains the major obstacle for patient access. Without funding, the patient simply cannot afford the treatment. This problem was noted in a report by the CDD stating that the lack of a specialized orphan drug policy in Canada could cause the majority of orphan drugs to be denied approval for reimbursement through provincial formularies or private drug plans (Health Canada, 1997). This would greatly restrict access to EDRD for rare disease sufferers because of the financial burden the treatment would levy on them. Although the report acknowledged this problem, it offered no solutions.

Since the Canadian Drugs Directorate report, the EDRP has been replaced by a similar program, the Special Access Program (SAP). It allows rapid access (less

than 24 hours) to drugs not approved by Health Canada (Health Canada, 2008). The physician-initiated program allows for treatment of life-threatening diseases for up to six months, at which time a new application must be submitted (Health Canada, 2005). Physicians must also provide a report on the effects of the drug on patient health. The final decision to supply the drug is the manufacturer's to make. It may impose restrictions on use or assure payment requirements are met before providing the drug. On many occasions, the manufacturer will provide the drug free of charge; however, if it does charge for the drug, a significant cost is levied upon the patient, patient's family, hospital or a public or private drug insurance plan (Health Canada, 2005). Orphan drugs often cost upwards of $250,000 per year; quite a heavy toll for access to a life-saving treatment (Clarke, 2006).

Past major federal health reports have also supported development of a system that provides reimbursement for expensive drugs. The Romanow and Kirby reports both recommended that no Canadian should bear undue financial hardship because of the cost of prescription drugs, or because of where they are located in Canada. Although the Romanow (2002) report did not mention orphan drugs in particular, it did recognize the rising costs of prescription drugs and suggested a catastrophic drug plan that would have the federal government reimburse 50% of drug costs to the provincial drug plan if the drug costs over $1,500 per year. The individual would provide up to $1,500 per year, with the provincial and federal governments covering the rest of the expenses. The Romanow Commission saw this as the first step to a prescription drug coverage becoming integrated into the Canadian Health Act.

The Romanow Commission also suggested the creation of a National Drug Agency to: 1) negotiate and monitor drug prices, 2) set up an early warning system to

deal with developing expensive therapies, and 3) establish a national drug formulary to ensure that reimbursement decisions are made based on current evidence. However, none of these recommendations has been put in place. Instead of a national drug formulary, provinces have been negotiating their own drug prices. This may be due to the high cost of the catastrophic drug program as the Romanow Commission calculated that the program would require an annual increase of approximately $1 billion through the Canadian Health Transfer (CHT). Although the Commission's recommendations would have provided a step in the right direction, the high cost of EDRD may have prohibited provinces from covering them. Also there were no recommendations to improve research and development (R&D) of EDRD in Canada.

The Kirby report (2002) suggested programs similar to those discussed in the Romanow report including a national drug plan and protection from severe drug expenses. Kirby proposed a program that would put caps on out-of-pocket expenses, deductibles on private plans, and annual caps on drug expenditure. He also suggested that the federal government cover 90% of drug expenses that exceed $5,000 per year, with the provincial governments covering the remaining 10%. Individuals with a private drug plan would not pay more than $1,500 per year, with the federal and provincial governments covering the excess cost (90/10 split, respectively) above $5,000. Like the Romanow report, however, these recommendations have not become a reality. Kirby's recommendations would cost approximately $500 million a year, half that of Romanow's recommendation, but apparently still high enough to scare policy makers. Due to the lack of action on these proposed policies, many Canadians remain without coverage that would protect them against the heavy burden of expensive drugs.

In 2004, the Prime Minister and the first ministers gathered to discuss methods to improve health care in Canada. A priority was to set nationwide goals to help Canadians gain access to expensive pharmaceuticals (Federal, Provincial & Territorial Task Force (FPTTF), 2006). They reaffirmed that no Canadian should suffer financial hardship due to the cost of a needed drug, and that access to a drug should not depend on the province in which one resided in. To accomplish this, nine elements for a National Pharmaceuticals Strategy (NPS) were outlined including several that related to access and price control of EDRD. A commitment to specific goals with a designated time frame to accomplish these goals was detailed. The goals included developing a plan for catastrophic pharmaceutical coverage with methods to assess effectiveness and cost options, accelerating access to breakthrough drugs (including EDRD), and establishing a national formulary to ensure equal access across the country.

In order to implement the entire strategy, including increasing access to necessary drugs and to develop a catastrophic drug coverage program, the NPS recommended a contribution of $36 billion over five years (FPTTF, 2006). This much larger number is not to be compared to Kirby's and Romanow's estimates, which were only for expanded drug coverage. This has not happened. In 2006, the accord was amended and a 10-year plan was drafted to develop the NPS; however the funding proposal changed from the $36 billion over 5 years to $41 billion over 10 years with a specific directive to develop a catastrophic drug coverage program (FPTTF, 2006).

In 2006, a ministerial task force was appointed to investigate the best approach to health-care renewal; however, the NPS was immediately criticized for

not moving forward more quickly on the initiative (MacAdam, 2008). The task force was appointed to investigate, among other things, the development of catastrophic drug coverage and the establishment of a national drug formulary, and to facilitate quicker access to breakthrough drugs (which includes EDRD). The goals of this task force were very similar to those suggested several years earlier in the Kirby and Romanow reports. The task force published a report later that year that removed some of its goals and further developed plans for drug formularies and funding options for EDRD and a catastrophic drug program (FPTTF, 2006). The report stated five items of the strategy would be given priority including EDRD and a catastrophic drug program. However, accelerating access to breakthrough drugs (which also includes improving early access to EDRD), was dropped from the priority list.

There has been no significant progress with the federal government or industry since the report in 2006 (MacKinnon & Ip, 2009). In 2008, the task force created decision points that would be a focus for progress, which included a Canadian access program for EDRD and a national Pharmacare program. The Canadian access program for EDRD would include a transparent decision-making model with public input, similar to the European Union's citizen's council. Furthermore, there would be a 50/50 cost sharing split for drug costs, and a national registry for researching and monitoring drug effectiveness. Overall, the progress of the NPS has been slow and not encouraging. In early 2009 the Health Council of Canada (HCC) published two reports on the status of the NPS and criticized the slow progress. The HCC recommended alternative strategies to reignite the strategy and achieve key elements including catastrophic drug coverage that would help individuals with rare disease access their much needed expensive medications (HCC, 2009a, HCC 2009b).

Unfortunately, there has been no official response from the provinces or federal government to the reports. Currently, there are various provincial initiatives in Alberta, B.C. and Ontario being developed to improve patient access to expensive therapies. However, many provinces have not moved on this issue, further exacerbating the regional variations in drug access.

2.5 Canada's Centralized Drug Review Process

Since 2003, The Common Drug Review (CDR) has served as a centralized body for providing recommendations of drug reimbursement for federal and provincial drug plans. Quebec is an exception in this regard as it has its own provincial drug review process. The CDR process is managed and overseen by the Canadian Agency for Drugs and Technologies (CADTH). It is the CDR directorate that makes recommendations concerning pharmaceutical treatment reimbursement (CADTH, 2007). A CDR expert subcommittee reviews and summarizes the available clinical and pharmacoeconomic evidence about the drug that comes from the manufacturers, and both published and unpublished literature (CADTH, 2007). The subcommittee then passes the information on to the Canadian Expert Drug Advisory Committee (CEDAC), which is "an appointed, national, independent, body of physicians, pharmacists and other health care professionals and public members." (CADTH, 2007, p.5) CEDAC reviews the information from the CDR and then makes recommendations available to the federal and provincial formularies whether to list, not list, or list with criteria particular drugs on their formularies. Each province then decides independently whether to fund the drug. Provincial drug plans have agreed with the CDR recommendations more than 90% of the time (CADTH, 2008). All

CDR recommendation decisions, status of submission and CDR processes can be accessed by the public on this website: (http://www.cadth.ca/index.php/en/cdr).

The CDR bases its recommendations on three criteria founded on a systematic review of clinical evidence, and an assessment of the pharmacoeconomic data. These criteria include: 1) clinical studies that assess the efficacy of the drug in appropriate populations, 2) the therapeutic advantages and disadvantages relative to current therapy, and 3) the cost-effectiveness relative to accepted therapy based on pharmacoeconomic calculations (CADTH, 2009). Costs of patented medicines are regulated by a central, independent authority, the Patented Medicines Prices Review Board (PMPRB). The PMPRB sets the maximum amount a manufacturer can charge per dose; however, the wholesalers and retailers can charge prices above the manufacturer's price. The CDR bases its cost effectiveness calculations on the prices set by the manufacturer after it has been approved by the PMPRB (PMPRB, 2009). Using guidelines and templates that help ensure rigor and consistency in all reviews, the CDR begins its assessment by reviewing the evidence of health outcomes for the target population (CADTH, 2008). This is done before cost effectiveness is considered. This criterion is not only a problem for rare disease but can be for all drugs if they do not have enough clear evidence of health outcomes. For example, Fabrazyme® and Replagal® were not recommended for listing because of lack of meaningful clinical evidence of health benefit in randomized trials, along with their high cost.

In most cases, the second criterion of therapeutic advantage is a not a consideration for EDRD because most are breakthrough drugs, and cannot be compared to other existing therapies because there usually are not any. In some cases,

such as in treatments for some rare types of diabetes (i.e., diabetes insipidus), there exists a common treatment that is cheaper but much less effective. In these cases, the CDR often does not recommend the orphan drug because of cost (Milne, 2007).

Cost-effectiveness is the major obstacle for EDRD (Chambers, 2006). Research and development is expensive and the market is very small; therefore in order to make the drug a commercial success, companies charge very high amounts for EDRD. This often makes the drug too expensive to recommend for reimbursement (Wong-Reiger, 2007). The CDR uses pharmacoeconomic methodologies for assessment. These are analyses that incorporate many theoretic constructs (e.g., Quality-adjusted life years) into the equation (Moore, Ries, Foget, Schiffmann, 2007). The presumption is that the cost-effectiveness approach must incorporate the benefits the drug has in improving everyday life of the individual. The equations used for the CDR are more suitable for common drugs for diseases with a better known course and treatment effects, rather than rare diseases that may have more complex and heterogeneous symptoms. Efforts have been made to develop pharmacoeconomic methods that are more applicable for evaluating EDRD, including formulas to evaluate whether treatment for Fabry disease would be cost effective (Moore et al., 2007). To date, no acceptable formula has approved funding of enzyme replacement therapy for Fabry disease, which costs upwards of $300,000 per year.

Between September 2003 and December 2005, the CDR did not recommend public funding for any expensive drug for rare diseases (Clarke, 2006). Thirty-three new drugs were reviewed by the CDR during that time, 14 were recommended. Six of the 19 not recommended were treatments for rare diseases (Clarke, 2006). There is a threat of two-tiered access developing: those with private drug plans may get access,

while those relying upon public drug plans or without any coverage do not. h The final decision regarding reimbursement lies with the provinces, however, no drug for rare disorders has been approved by a Canadian public drug plan without strident patient advocacy; which often results in political decisions for individual patients (Clarke, 2006). The situation in Canada is that ill patients themselves must lobby to be treated.

Recently, attempts have been made to clarify the reasons for CDR decisions, such as allowing the manufacturer to review all their reports before submission to the CEDAC. This information is also posted on the CADTH website (www.cadth.ca), along with a plain language description of the decision (Tierney & Manns, 2008). Overall, it has become increasingly evident that the CDR's evaluation method was not well developed for assessment of EDRD. Until a separate body is created, or new criteria and formulas are developed, individuals with rare diseases will continue to go untreated or be burdened with heavy financial costs.

2.6 International Rare Disease Policies

Most developed countries including the U.S., the European Union, Japan, and Australia have developed some form of ODP that facilitates the research and development of orphan drugs, which can reduce costs and increase innovation (Haffner, Torrent-Farnell & Maher, 2008). Without such policies, many orphan drugs may not have been developed (Haffner, et al., 2008). Some policies are more developed than others, and some have resulted in unintended problems, such as companies taking advantage of market incentives, but most have market incentives for pharmaceutical companies to participate in the orphan drug industry (Health

Canada, 1997; CORD, 2005; Haffner et al., 2008). Due to the absence of such policies in Canada, patients suffering from rare diseases often do not have access to potentially life-saving treatments that are available in countries with some form of ODP implemented.

Although not all international policies are feasible in Canada, they do provide a learning resource for Canadian policy makers. Several countries, such as the United States and Japan, have an ODP that controls the pricing of orphan drugs through R& D incentives such as tax breaks and market exclusivity agreements (Health Canada, 1997). The success of ODPs in other developed nations should encourage Canada to pursue development of its own either independently or in cooperation with other countries.

In the U.S., incentives developed through the Orphan Drug Act (ODA) of 1983 have allowed for small biopharmaceutical companies to develop orphan drugs and maintain a profit (USFDA, 2007). Provisions in the orphan drug act allow for: 1) financial support during the research and development phase, 2) support during the clinical trials phase, and 3) up to 50% tax cuts. *Scientific American* (Maeder, 2003, p. 81) praised the U.S. ODA as the "the best model devised so far." The strength of the U.S. ODA is that it sparked development of EDRD; between 1983 and 2006 the U.S. act resulted in 1,713 orphan product designations and granted 305 orphan drugs market approval (Haffner et al., 2008). The major weakness of the U.S. ODA is that there are no restrictions on the prices that can be charged for the drugs, leaving many too expensive for out-of-pocket payers. The absence of any price controlling mechanisms has defeated "the purpose of legislation which is to ensure that those patients that need life-saving or life-enhancing products have access to them"

(Cheung, Cohen & Illingworth, 2004, p. 192). This is the case even for those who have private insurance because the premiums become too expensive or the life-time maximum coverage is exceeded (Cheung et al., 2004).

Japan recognized the need for an ODP in 1985, when it allowed a special application process for companies submitting approval for EDRD (affecting less than 50,000 people in Japan) (Scott, Alder, Etusko, & Lui, 2001). In 1993, Japan launched an official ODP which allowed biopharmaceutical companies involved in orphan drug research to benefit from: 1) a 10-year market exclusivity agreement for their products 2) a priority review (Thamer, Brennan, & Semansky, 1998); 3) research and development incentives (Thamer et al, 1998); and 4) tax credits for research and development of up to 10% (Thamer et al., 1998). The implementation of these incentives has resulted in over 100 orphan drugs being approved in 10 years (CORD, 2005).

In order to control profit margins of pharmaceutical companies in Japan, the government placed a stipulation that if a company makes a yearly profit over $100 million yen (almost $1.2 million CAD), then it must pay a 1% sales tax on that profit until the government subsidies have been repaid (Cheung et al., 2004). Japan also has a centralized agency cosponsored by the government and the pharmaceutical industry, known as KIKO (Scott et al., 2001). KIKO reviews applications for the incentives, and if approved, provides them along with the Ministry of Health and Wellness through their shared funding arrangement (Scott et al., 2001).

The European Union, under the European Medicines Agency, has developed several policies regarding orphan drugs such as: 1) protocol assistance (scientific advice during the product-development phase); 2) marketing authorization for a 10-

year marketing exclusivity; 3) financial incentives (i.e., fee reductions or exemptions); and 4) national incentives detailed in an inventory made available by the European Commission (from European Medicine Agency's Press Office, 2007).

The United Kingdom has a National Institute for Health and Clinical Excellence (NICE) as part of the National Health Service (NHS). It is an independent organization made up of health professionals, patients, industry, academics, and the public. NICE's mandate is to provide guidance to the NHS on health promotion and illness prevention, and treatment in the areas of public health, health technology and clinical practice. NICE uses scientific and social value judgments when making health-care decisions. Within NICE is the citizen's council, consisting of 30 members who have experience with the NHS but who are not health-care professionals. The members vary in age, gender, race, socio-economic status, disability, and ethnicity. In 2004, the council held a three-day conference to make decisions regarding EDRD. In the subsequent report, the council had a majority vote to use a different way of assessing value for EDRD than common drugs. Members determined that the main criteria to take into account when assessing whether to pay premium prices for EDRD were the degree of severity of the disease, the health gain the treatment will provide, and whether the disease is life threatening (NICE citizens' council report, 2004).

In 2009 the European Commission, consisting of member states, took the recommendations of the NICE's citizens' council further and released recommendations on how to take action in the field of rare diseases. In the report, the council decided on a variety of actions including officially recognizing rare diseases as being a significant threat to citizens of the European Union, and making it of paramount importance to the member states to implement policies that would improve

research and access. Included in its recommendations were plans to integrate research centers around the Union to facilitate them working together. Additionally, there was a plan to develop a classification and codification system and integrate it into a European reference network that helps identify rare diseases earlier by collecting information throughout the European Union. The Council also recognized the importance of citizen involvement as a "prerequisite for health" and encouraged development of strategies to incorporate patient involvement in its care (European Commission, 2009).

Although criticized for its slow progress, (Joppi, Bertele & Garatinni, 2006) the European Union's new initiative has recognized 443 orphan drug designations and approved 31 orphan drug products for marketing during its first six years of operation (2000-2006) (Haffner et al., 2008). This progress is even speedier than the early developing years of the orphan drug act in the United States.

The European Agency for Evaluation of Medicinal Products (EMEA) is the European Union's centralized body responsible for administrating orphan drug legislation. EMEA serves as a cost saving mechanism for member countries and the pharmaceutical industry by streamlining the application and approval process (Cheung et al., 2004). Additionally, an amendment was made to the ODP that would strip drugs of their orphan status after a five-year period if the companies have made a significant profit from the drug (Cheung, et al., 2004). This amendment helps guard against manufacturers taking advantage of the ODP for profit.

Several other ODPs have followed in the footsteps of the U.S. and Japan. Other countries such as Australia and Singapore allow for an expedited review process to provide quicker access to the drug for patients, exclusive market rights to

the drug for a period for up to 10 years, and/or a global market for product distribution that provides further incentives for biotechnology companies to pursue treatments of orphan drugs. For example, FDA-approved EDRD are given an exemption from evaluation in Australia, meaning they are not assessed for safety and effectiveness in Australia if they have been approved by the FDA. This process reduces costs and can lower prices. It also allows for quicker patient access to the drugs (Scott et al., 2001).

ODPs have been criticized for serving private industries' interests over the interests of patients (Haffner, 1999). Market exclusivity "creates an attractive monopolistic market for companies interested in developing a product for any given rare disease" (Cheung et al., 2004, p. 185). This monopoly along with no price regulation policy can often make drugs for rare diseases unaffordable for any patient not on government health coverage or private insurance plans.

2.7 Nongovernment Recommendations

The Canadian Organization for Rare Disorders (CORD) (2005; 2007) has recognized Canada's situation and suggested prototype policies for orphan drugs that may help the development of such policies. CORD is a national network for organizations representing those with rare disorders; it advocates for a health-care system and policies that work for those suffering from rare disorders. CORD emphasizes the need for fast tracking of new drugs to treat those in life-threatening conditions, and conditional approval based on limited clinical evidence. It also suggests that there be a reduction in fees for pharmaceutical companies researching drugs with small market potential because currently there is little to no research or

development of EDRD in Canada. The inability of the CDR to assess EDRD is also recognized by CORD and it suggests that EDRD be outside the jurisdiction of the CDR.

BIOTECanada (2004; 2007) is a leading biotechnology R& D firm in Canada, and like CORD, it has continually reported the need for a Canadian ODP. BIOTECanada advocates that an ODP must incorporate the whole life cycle of EDRD from R&D through approval, to access and assessment. It argues that key components of any ODP must include competitive incentives for R & D companies to bring new therapies to the market in conjunction with promises that the prices of the drugs be reflective of the incentives. Like CORD, BIOTECanada believes that EDRD evaluation should be outside the authority of the CDR.

2.8 Provincial Initiatives

The most affordable drug programs in Canada for patients who suffer from a rare disease are in Alberta and British Columbia, the only two provinces with policies specifically identified as rare disease drug programs. Although this is a benefit to patients in Alberta and B.C., it creates unequal access for patients across the country.

Alberta's program, which began April 1, 2009, covers disease such as Fabry disease, Gaucher's disease, Hunter disease and Pompe disease, with additional treatments for other rare diseases being reviewed by an expert drug committee. Although patients are required to pay an unspecified premium and to make co-payments, the provincial government funds the majority of the drug cost (Government of Alberta, 2008). Little information has been released thus far on

Alberta's program; therefore it is difficult to comment extensively on it. However, it is a new program and more information may be released in time.

British Columbia has a Pharmacare program that allows patients access through a physician's recommendations to the lowest cost therapies for rare diseases. Often rare diseases only have one treatment, therefore choosing an appropriate drug is not an issue (Government of British Columbia, 2007). The provincial government does mention several times in its annual report that it hopes for a national ODP to create equal access for patients across Canada, however it has placed reliance on the NPS for further action.

Ontario has several policies in place, such as the Trillium Drug program and the Ontario Drug Benefit: Exceptional Access Program, however, it does not have an official provincial ODP. Generally drugs need to be listed on the formulary to be accessible for coverage (Government of Ontario, 2008), but many EDRD are not recommended by the CDR thus many do not get listed on the provincial formulary. However, there is a physician-initiated Exceptional Access Program that allows physicians to apply for a limited time coverage of a drug not listed on the formulary. Additionally, the Trillium program only covers a partial amount of the drug cost, and cannot be used if private insurance is used in the household, which leaves some patients with high out-of-pocket expenses.

The Trillium drug program only covers individuals over 65 and receiving long-term care or social assistance (Best Medicines Coalition, 2003). The program was developed to cover high drug costs in relation to patient income, but again, the costs are too high for orphan drugs. Although the attempts made by the Ontario government are not the complete solution to the problem, they provide a framework

upon which other provinces can build.

2.9 A National Approach: The Canadian Fabry Disease Initiative

This background brings us to the most recent initiative and the focus of this research, the Canadian Fabry Disease Initiative (CFDI). Until 2000, treating the symptoms was the only solution for people with Fabry disease. In 2000, two drugs targeting enzyme replacement therapy (ERT) were provided as a treatment for this rare condition: Replagal® (agalsidase alfa; manufactured by The Shire Human Genetic Therapies Inc.) and Fabrazyme® (agalsidase beta; manufactured by Genzyme Corporation). Both have been approved for use based on safety and effectiveness in most developed countries, including Canada. However, neither drug was recommended by the CDR in 2005 because of lack of cost effectiveness, limited meaningful clinical outcomes and no evidence that they improve quality of life. After this decision, the manufacturers stopped providing treatments for patients without payment (which they had been doing through special access program), and patient outrage ensued (Bichet, Casey, Clarke, Sirrs & West, 2008; CIHR, 2008). Patients participating in clinical trials continued to receive the treatments while most who were receiving it on a compassionate basis were taken off the drug. Most patients in B.C., Alberta and Ontario remained on the treatment; however, the major concern was for patients in Nova Scotia. A large portion of Fabry patients reside in Nova Scotia and the Nova Scotia government would not provide reimbursement for treatment. Therefore, Fabry patients in Nova Scotia went without treatment for over a year.

In late 2005, the federal and provincial governments responded to increasing demand from Fabry patients to have access to treatment. Their answer was to provide them with the ERTs through a clinical research study model called the Canadian Fabry Disease Initiative (CFDI). The CFDI was developed as a cost-sharing arrangement between the federal and provincial governments and the manufacturers (The Shire Human Genetic Therapies Inc & Genzyme Corporation). Funding was established for a three-year clinical study that would provide the drugs to patients on a national platform and assess the two treatments for Fabry disease (Bichet, et al., 2008). Nothing public is known about the details of the cost-sharing relationship.

The CFDI was viewed as an important initiative because it may serve as a model for funding and researching EDRD in Canada (Bichet, et al., 2008). The Canadian Fabry Disease Initiative (CFDI) is a clinical research study, with five research sites across Canada, in Halifax, Calgary, Vancouver, Toronto and Montreal. The CFDI infrastructure consists of a lead physician, nurses and coordinators at each regional site. The patients are randomly assigned to receive either Replagal® or Fabrazyme® every two weeks. There is no control group. Patients are infused with ERT in a clinic, in a hospital or at home. Data, including medical history, electrocardiograms, eye exams, pain questionnaires, and other lab tests are collected for each patient at each site on a regular basis. This data is then sent to a national coordinator who incorporates all data into a centralized database.

The CFDI is designed to include individuals with Fabry disease, who have consented to participate, into one of three cohorts. Cohort 1a is for patients who have received or are still receiving ERT before the CFDI. These patients remained on the same treatment they were provided before the CFDI. Cohort 1b includes Fabry

disease patients who meet ERT treatment guidelines, as published by the Garrod Association (2005), with either of the two ERTs. Patients in cohort 1b are randomized to one of the two drugs. Cohort 1c includes patients who have Fabry disease but do not meet the Canadian treatment guidelines for ERT. If Cohort 1c patients develop more severe symptoms of Fabry disease and meet the Canadian treatment guidelines then they are moved to Cohort 1b and randomized to an ERT.

The CFDI was developed with five major goals (from the Canadian Fabry Research Consortium, 2009): 1) to establish a national registry that will collect information related to the identification and monitoring of all persons with Fabry disease in Canada; 2) to determine the degree to which existing complications of Fabry disease respond or fail to respond to ERT; 3) to determine the impact of ERT on the development of complications of Fabry disease in men and women who are on ERT or whose ERT was interrupted; 4) to identify which of these clinical problems can best predict the outcome of ERT on Fabry disease; and 5) to identify possible side effects of ERT.

Although not identified by the Canadian Fabry Research Consortium as one of the goals, investigators have identified a sixth outcome goal: to conduct a direct comparison of Replagal® and Fabrazyme® at standard dose. Thus far, the CFDI has already succeeded where other initiatives, such as those proposed by the Romanow, Kirby or NPS, have failed because it has been implemented and provides national coverage for an EDRD for the first time in Canada.

An additional component the CFDI is to ensure, as recommended by the CIHR, Fonds de la recherché en santé du Québec (FRSQ) and Health Canada, is that the study's goals are accomplished using procedures and protocols of internationally

accepted standards of scientific excellence (CIHR, 2008). To accomplish this, the Independent Scientific Oversight Committee (ISOC) was developed "to monitor, evaluate and communicate publicly the results of the research" (CIHR, 2008). The ISOC assessments are based on the annual progress reports submitted by the CFDI research teams, any ad hoc submission of proposed amendments to the study protocol, and reviews of copies of the CFDI Study Data and Safety Monitoring Board reports (CIHR, 2008).

Thus far there have been two reports from the ISOC for the years 2006-07 and 2007-2009. The 2006-2007 report determined that adequate progress had been made given delays in funding, hiring of staff, and signing of contracts. Such delays were attributed to the absence of a single study sponsor. A study sponsor would have control over the maintenance of the study. The ISOC and the CFDI research team recommended the CIHR to be the sponsor. The CIHR declined, stating it was not in a position to "exercise control over carrying out of the study" (CIHR, 2008). The main role of the CIHR is to administer the federal contribution of funds, and to assure that the CFDI is conducting research with standard policies and practices. It does this through the ISOC. The ISOC also stated that all ethical requirements were being met and that other concerns (for example, defining clinical goals, developing a statistical plan, and randomization) will be addressed as the study continues. A little over a year later the second report was completed. In this report the ISOC identified several data problems, such as incomplete data and accuracy of data; however, the committee was satisfied with the overall progress of the CFDI (Hollak, Mitchell, Muenzer & Wraith, 2009). The second report also found similar findings to the previous year's, such as: lack of sponsor and long-term funding are major issues that should be remedied, and

that the CIHR should be the sponsor was reiterated. The evaluation study proposed here uses qualitative research methods to evaluate the CFDI. This approach will use a holistic-inductive approach as recommend by Patton (2002) as a method to understand the program as a whole. This should complement the findings from the ISOC evaluation.

2.10 Significance of Research

As indicated, the development of a Canadian orphan drug policy has garnered more attention in recent years. The CFDI is an example of a program that has the potential to be implemented as an intervention to improve patient access to EDRD. It is an innovative approach to increasing data on the effectiveness/side effects of EDRD (in this case enzyme replacement therapy) through a publicly funded research study, while improving patient access to the drug and gathering further information on the idiosyncrasies of Fabry disease. To date, there has been no effort to evaluate the program using qualitative research methods from a holistic perspective. CIHR and ISOC published their only CFDI report in 2008 that assessed the CFDI's activities in 2006-2007. However, their evaluation was based on reports provided by the CFDI research team and did not consider opinions from other affected parties. This study takes a different approach and has a different methodology. It is designed to use a qualitative content analysis approach to evaluation as recommended by Greene (1994) and Patton (2002) to provide useful and meaningful information to decision makers and information seekers about the CFDI.

Specifically, the study objectives of the current research are to explore key informants' perspectives on the CFDI, using semi-structured interviews, in order to:

1) assess whether key informants perceive that the CFDI is meeting its goals and objectives; 2) determine if the key informants believe the CFDI is a model that can be applied to other treatments for rare diseases; 3) provide recommendations, developed from a variety of perspectives, that could improve the CFDI; 4) gather perspectives as to whether the ISOC is contributing to, or detracting from, the CFDI; and (5) understand whether the key informants believe resources given are appropriate for the study.

"Key informants are individuals who possess special knowledge, status, or communication skills, who are willing to share their knowledge and skills with the researcher, and who have access to perspectives or observations denied the researcher through other means" (Gilchrist & Williams, 1999, p. 73). Within this context, the key stakeholders are CFDI investigators, patients enrolled in CFDI, pharmaceutical providers and government officials involved in drug policy. These groups were chosen because they possess the knowledge and varying perspectives that the researcher requires to provide a holistic evaluation of the CFDI.

As an innovative study, the CFDI may have an important role in the development of a national orphan drug policy or other programs in Canada. It can also serve as a prototype study for gathering scientific data about treatments to inform future decisions about treatments in Canada. By using content analysis to qualitatively evaluate the CFDI, this study will help determine how the program is progressing, identify what problems exist from different group perspectives (i.e., patients, CFDI investigators), and investigate how it adapts to adversity. As mentioned, the only scientific evaluation of the CFDI occurred by the ISOC for the year 2006-2007, but the ISOC could not assess many aspects of the CFDI because of

delays in progress at the time. It is prudent to make efforts to ensure programs such as the CFDI are delivered in an effective and acceptable manner to all those that it affects. This can be determined qualitatively by continual evaluation from important stakeholders, and independent practitioners with interest in the program. This research provided this opportunity by application of a content analysis methodology to a key informant evaluation as suggested by Patton (1980, 2002). The following chapter further describes the importance of qualitative evaluation in health policy and the use of content analysis theory as a methodology. It will detail the study design, study protocol and methodology.

CHAPTER 3: METHODS

3.1 Study Design

Qualitative methods are of great value in program evaluation because they can provide a rich description of the intervention being evaluated, resulting in an inclusive depiction of the intervention's usefulness (Patton, 1980; Sofaer, 1999). An evaluation of the progress through the first two-and-a-half years of operation will provide additional knowledge to decision makers and information users (Patton, 1980).

The research design employed for this study is a qualitative social program evaluation (Greene, 1994). The study was conducted using a semi-structured emergent design in order to evaluate the Canadian Fabry Disease Initiative based on responses from various key informants. The study was granted ethics approval by the Health Sciences Ethics Committee of Dalhousie University in Halifax, N.S., Canada (February, 2009).

Interviews, the main source of information for qualitative evaluations, served as a useful method to identify patterns and configurations, and ultimately provided a detailed description of an intervention, in this case the CFDI. Specifically, a qualitative program evaluation using a content analysis approach is an effective method to look at a project's merit, assess its worth, and provide feedback to program operators (Patton, 1980; Sofaer, 1999).

From an epistemological standpoint, it is essential to establish a methodology and a method before conducting an analysis. As Carter and Little (2007) report, this is a necessary step to "provide a framework for planning, implementing and evaluating

the qualitative research" (p. 1316). Epistemology is the theory of knowledge (Carter & Little, 2007); therefore the choice of what knowledge to obtain had to be determined. This will shape the way beliefs about the information are developed and maintained. As Carter & Little (2007) indicate, the goal is to engage with peoples' subjectivity and allow ones' experiences to "jointly create" (p. 1319) knowledge with the participants. The development of the research questions helps focus the content under a lens of CFDI evaluation from the participants' perspective.

All responses from key informants are valid and given merit because it is their perspective that the researcher wishes to gain, however the responses must be clarified as to whether the information provided is true, if it is their opinion, or if it is a belief that the individual holds. It is the responsibility of the researcher to look into suspected incorrect statements in order to determine if the information being presented is factual or is untrue. This requires further research into the specific comments made by individual respondents if the data has emerged as a dominant theme.

Miles and Huberman (1994) provide a well-articulated description of the methodology of content analysis. Pope and colleagues (2000) also provide a well-designed framework for content analysis. Using both frameworks for guidance, recurrent themes in phrases provided by participants were explored and analyzed for important information. Exploration of the text occurred both within and between subjects to develop codes to delve deeper into the text to combine related material from different sources regarding topics that had the same root meaning. A more in-depth description of content analysis will be provided in the Chapter three, section six.

A methodology is the theory and analysis of how the research should proceed. It is the justification of methods. Both procedures mentioned above, as well as others used to describe the process of extracting knowledge using content analysis, were guiding methods for this study (Pope et al., 2000; Miles and Huberman, 1994; Bereska, 2003, Cote, Durand, Tousignant, & Poitras, 2009). The researcher conducted the interviews and took notes about the responses, then the interview was transcribed and the notes written in a more formal and readable manner. The transcripts were inputted into Atlas.ti for review. Atlas.ti is one of the most popular software packages used to manage qualitative data (Pope, et al., 2000). The information gathered from previous interviews was used in subsequent interviews to ask additional questions or provide information that emerged from the previous responses. Between interviews, transcripts were read and reread while additional notes were written. The new notes were then reviewed along with older transcripts and notes for similar ideas. The transcripts were then reread with these new ideas in mind, and previous and further transcripts were also reread when any new ideas or themes emerged. This process continuously occurred with new interviews and with new information until no new information emerged from the texts (as suggested by Pope et al., 2000).

3.2 Recruitment of Participants

Key informants need to be individuals who possess special knowledge of a program (the CFDI) and are willing to share their knowledge through a means that is not available elsewhere (Gilchrist & Williams, 1999). In this case, key informants were those with firsthand knowledge of the CFDI, through involvement of the infrastructure, experience as a patient, or expert experience with the policies that

developed the CFDI, or they were involved in the provision of drug. Inclusion criteria for key informants were that they were: a) employed by the federal government, b) employed by the provincial government, c) employed by a pharmaceutical company, d) a member of the Canadian Fabry Association, e) a patient enrolled in the CFDI, f) an investigator, coordinator or nurse working for the CFDI or the ISOC, and that they g) had experience with the CFDI development or protocol procedures. The final item is added as a qualifier because not all provincial or federal government officials, nor all pharmaceutical representatives would have knowledge of the CFDI, and thus would not be a valuable participant.

CFDI investigators were chosen from the contacts list identified by the Canadian Fabry Research Consortium (2008). This consortium is a group of clinical researchers at regional research centers in British Columbia, Alberta, Ontario, Quebec and Nova Scotia. The ISOC members were identified by the Canadian Institute for Health Research (see http://www.cihr-irsc.gc.ca/e/35802.html). The Canadian Organization for Rare Disorders (CORD), the patient representative group The Canadian Fabry Association (http://www.fabrycanada.com) and pharmaceutical representatives (from Shire Human Genetics Therapies Inc, and Genzyme Corporation) were contacted. Requests were made for anyone within their organization interested in participating to contact the primary investigator of this study. All contact was made via email or telephone. If the individual chose to participate, an information package was made available to them regarding details of the study.

In accordance with the Tri Council Policy Statement, and using recommendations from the CIHR (2005), the current study used an opt-in consent

process. Prior to the start of the research, individuals were informed of the research and its objectives, and given clear indication that they agreed voluntarily to participate in the research and could voluntarily withdraw at any time. This was indicated in writing by signing a consent form.

3.3 Data Collection

Data were collected using a semi-structured qualitative interview, a significant component of many qualitative studies and the most commonly used method of data collection in qualitative research (Dicicco-Bloom & Crabtree, 2006). Therefore, unstructured interviews with key informants were intended to uncover novel information regarding their personal perspective of the CFDI. All participants were presented evaluation questions (for questions see Appendix A). Any questions that arose during the course of interviews or that emerged through the ongoing analysis of data were also presented (see Appendix B for emergent questions). Interviews consisted of the principal investigator (PI) presenting each participant with a series of open-ended questions designed to elicit the participant's knowledge, opinions and beliefs of the CFDI, possible improvements for the program, and its potential applicability of use for other EDRDs. Responses obtained from all perspectives were considered, and developed into recommendations for the CFDI and government decision makers that plan to develop similar initiatives. Probing questions followed the initial responses to clarify responses and to gather more in-depth information on particular topics.

Based on qualitative standards (Politz & Beck, 2004), it was the goal of the PI to obtain responses from a minimum of one pharmaceutical company representative

and government official, four CFDI investigators and patient representatives, and two members of the ISOC . Attempts were made to recruit more participants, within the time and budget constraints. This was deemed an appropriate number for a qualitative study of this nature (Politz & Beck, 2004).

All participants were contacted via email or by referral from other participants. In the email, the participants were informed of the purpose of the study and what was required of them if they chose to participate. Participants agreed to this procedure over email before the interview and afterward in a letter of consent that was mailed to them with a return envelope enclosed. Participants were assured at the beginning of the interview that their identifying information would be held in confidence and all information will be reported anonymously. The PI conducted all the interviews. After the interview, the data was downloaded to a password-protected database, for which only the PI had the password. The sound recorder was locked in a drawer in the office of the PI. The PI also transcribed the interviews and saved the document in the same password-protected database.

Transcriptions of all interviews were reviewed by the PI, using Atlas.ti. All Atlas.ti documents were also saved on a password-protected database. The names of the respondents were replaced by a coded identifier that consisted of two letters followed by a four-number sequence and a final letter, for example (IT001A). This was done so that the second researcher who analyzed several transcripts and coded them for inter-rater reliability could not identify any participants by their transcript.

The transcripts were reviewed for recurrent ideas and themes, which were developed into concepts and categories and finally formed into a theory. The

development of emergent research questions (Appendix B) and important issues, problems, or ideas evolved through the analysis process as is described next.

3.4 Data Organization

During analysis, it is important to continually link the collected data with the research questions. Crabtree and Miller (1999) have suggested five steps necessary to interpreting and reporting the results of a qualitative research study, including: describing, organizing, connecting, corroborating/legitimizing and representing the account. The first step, "describing," involves the researcher temporarily removing himself/herself from the data and reflecting on its meaning and how he/she has influenced the analysis, then deciding what approach to use next. The next three steps (organizing, connecting, and correlating/legitimizing) together comprise the analysis phase. Finally, how to interpret and represent the data is part of representing the account and presenting the true meaning of the findings.

The choice of an organizing style is the first step to the analysis of the data. Crabtree & Miller (1994), suggest choosing one of three styles: template style, editing style, and immersion/crystallization style. These three options serve as starting points for analyzing the data and are not necessarily mutually exclusive. The template phase involves developing a code manual or template a-priori, however it is a flexible manual and codes can change as the data analysis progresses. The code manual is created based on a variety of available knowledge such as literature, self analysis or discussion among research team. This method is useful when there is prior knowledge on the topic of study (Crabtree & Miller, 1994). When using the immersion/crystallization style, the research skips the step of coding and becomes

deeply immersed into the texts until the interpretations form and become concrete or 'crystallized' theories (Crabtree & Miller, 1994). This style is suitable when there is little prior knowledge of the topic under question to draw any codes from.

The third style, and the one selected for this research topic, is the editing style. For this process, the researcher enters the analysis phase without any predetermined codes. Codes are created as the researcher is immersed in the data and information deemed important is extracted and coded (Crabtree & Miller, 1994). This method is also useful when little information is known beforehand, but the researcher chooses to develop codes during the analysis phase. In this case, information is available about the research outcomes and protocol of the CFDI, but little is known about individual perspectives of the CFDI from its investigators, patients, and funders (government and treatment providers). The editing style was complemented by using some characteristics of the template and immersion/crystallization styles. Similar to the template style, research questions were formed prior to the data collection which was used as a lens for directing questions and the beginning analysis, but no coding manual was predetermined to categorize emerging codes. The researcher spent an extensive amount of time reading and rereading the transcripts, listening to the interviews and reviewing analytic notes and memos through a process characteristic of the immersion/crystallization style (Crabtree & Miller, 1994).

After the initial phases of analysis which involved repeated review, data extraction and code development, the next step was connecting the extractions of data that lead to discovery of categories of data and the development of themes. Categories were made by examining the transcripts diligently and extracting parts determined to be important or appearing frequently within and between groups. Categories were

then further analyzed and grouped into emergent themes. These themes are described further in the results and discussion sections.

The next and especially important step in the process of data analysis is the corroborating/legitimizing step (Crabtree & Miller, 1994). This step is essential in making certain that the researcher has properly represented the research finding. To ensure proper reporting in this study the researcher continually returned to the original, coded and categorized texts to confirm that the reported explanation was representative of the participant responses, and to detect any possible mistakes or misinterpretation of texts. To protect against coding and reporting errors the process of code-checking was performed throughout the analysis process. Code checking, as described by Miles and Huberman (1994) is the process of coding a section of data, in this case an interview transcript, returning to the data several days later to code again, then comparing the two. This was useful, especially because only one researcher coded the majority of data. Through these steps the researcher made every effort to accurately describe and report the responses of the participants.

3.5 Qualitative Social Program Evaluation

Since the 1970's, evaluative methods using a qualitative approach have grown in popularity because of the limitations of quantitative-only approaches (Steckler, 1989). Currently, qualitative methods are often used to evaluate health services and health policy (Caudle, 1994). As described by Sofaer (1999), a great value of qualitative research is that this methodology has the ability to "enhance the capacity not only to describe events, but to understand why the 'same' event is often interpreted in a different, or sometimes conflicted manner by different stakeholders"

(p.1106). Applied to the CFDI program, this study attempted to document and describe the same program from different key informant perspectives by applying content analysis methodology to the interview transcripts.

A qualitative approach is an "integral aspect of evaluation" of social programs (Cronbach & Associates, 1980, p. 35) and is a unique form of social inquiry (Greene, 1994). A social program is created as a response to priority individual and community needs created through political decisions (Greene, 1994). The CFDI was created in that manner and therefore is a social program. Specifically, it was a response from the Federal and Provincial governments to the lobbying Fabry disease community and its physicians who reacted to the removal of affordable access to enzyme replacement therapy.

The CFDI was created through political means and its maintenance and ongoing implementation is subject to political pressures. This fact is illustrated by the threat of termination of the program without long-term plans for federal or provincial funding. The goal of evaluation is to make qualitatively based evaluation statements about the issues; for example, the problems, unchangeable factors and benefits of the program based on key informant responses to questions regarding their experiences with the program (Weis, 1987).

Gathering information from a variety of perspectives will help information users and seekers understand the program as a whole and provide a holistic description of the CFDI (Patton, 1980).

This evaluation is framed by the responses of the key informants to researcher inquiry about their experiences, and opinions of the program. In the use of qualitative program evaluation, key informants can also be identified as stakeholders, as defined

by Greene (1994). This method is used to obtain a perspective on the importance of specific components of the program and the experiences of key informant groups within the program. From this information, the evaluator can make value judgments about the worth of program areas to each key informant group and between all groups (Greene, 1994). As such, the varied stakeholder positions will represent the different values and political stances of each (Green, 1994).

This evaluation is considered an interpretivism evaluation (Greene, 1994). When conducting an interpretive evaluation the researcher uses an inductive approach to try to understand the various perspectives of the directors, staff and beneficiaries of a particular case study or program, most often using interviews. The researcher tries to use this information to make sense of the program without imposing preexisting expectations on the research process (Patton, 2002).

The ultimate goal of an interpretive approach is to understand how the program is experienced by the various people involved in it. In context of the CFDI, the primary physicians are viewed as directors, while coordinators and nurses of the program are viewed as staff. The patients and the pharmaceutical industry are viewed as the beneficiaries because they receive access to the treatment and reimbursement for the treatment, respectively. Government officials could also be viewed as beneficiaries because their citizens are receiving treatment or payers because they contribute to reimbursement.

3.6 Content Analysis Theory

Using the frameworks described by Miles & Huberman (1994) and Pope and colleagues (2000) in conjunction with Patton's (2002) recommendations, this study

used an ideal qualitative methods strategy composed of three parts: qualitative data (interview transcripts), a holistic-inductive design using naturalistic inquiry, and content analysis. Patton defines content analysis as any "qualitative data reduction and sense making effort that takes a volume of qualitative material and attempts to identify core consistencies and meanings" (p.453). Additionally, as recommended by Patton (2002), this study was designed to begin with specific data, such as individual interview transcripts and researcher notes to build toward a developed general pattern (within and between group themes). Interview transcripts are the most widely used form of qualitative data and their use was determined to be the best method to acquire the desired knowledge for evaluation (DiCicco-Bloom & Crabtree, 2006). Through the use of naturalistic inquiry, content analysis is a powerful method to do this (Patton, 2002). The form of inquiry in this study was naturalistic because it did not impose any predetermined course of questioning and it was an attempt to investigate the program in its naturally occurring state. There was no attempt to control or place constraints on the outcome of the research (Patton, 2002). Content analysis is the preferable method because the data used to support conclusions are found in and emerge from the raw data itself (Miles & Huberman, 1994; Corbin & Morse, 2003; Hermanowicz, 2002; Kvale, 1996; Soafer, 1999). This process is "of great value in studies of policymaking, of policy implementation, and even of policy consequences" (Sofaer, 1999, p. 1106). As is the case in this study, investigations using content analysis theory often consist of in-depth interviews resulting in transcripts of the interview which are rich sets of data.

The following is a description of the content analysis process provided by Patton (2002) and further described by Pope, Ziebland and Mays (2000). Data was

constantly compared and reviewed through systematic analysis of the texts and indexing of data. Ongoing analysis was done while transcribing, taking notes, reading, rereading, and reducing data. Through this process, codes emerged that helped the researcher recognize interconnectivity between participant responses (Allen, 2003). Qualitative research often consists of a daunting amount of data (i.e. transcripts) and therefore data reduction is necessary to make the information more manageable (Huberman & Miles, 1994). Data reduction is the process of extracting information from the text that is relevant to the topic, so that the information being reviewed is more concentrated and related to research questions or an important issue discovered during the analysis (Huberman & Miles, 1994).

With further analysis, the researcher became aware of and was able to identify particular words or phrases that highlighted important issues and allowed codes to emerge. Codes were labels used to identify responses from participants. When important information was reviewed it was given a code, and then when similar information was provided by the same or different participant the relevant code was applied. When a new code emerged, the researcher reread previous transcripts for relevant information regarding that code. Codes were then indexed and further refined to construct categories of codes based on similarities between them (Pope et al., 2000). Categories incorporated codes with similar meanings so that they were grouped together under a more descriptive heading. Categories were then further investigated and linked to uncover commonalities that helped develop themes about the CFDI (Pope, et al., 2000; Allen, 2003; Bereska, 2003). Themes were developed at a deep level of analysis and consisted of ideas and concepts that emerged from the

data within and between groups. Themes exist throughout the context and are used to develop theories and conclusions.

Throughout the analysis process codes and categories were divided into different analytic memos, based on context. The use of analytic memos is important because it was used to separate different and combine similar codes or categories onto a single sheet of paper or document. This is a reliable and replicable method to analyze interview data because it draws the conclusions directly from the raw data, which provides a firm foundation of support for the conclusions.

Existing frameworks for analysis by Pope and colleagues (2000), Miles and Huberman (1994) and Patton (1980) encompassed the broader levels of analysis through systematic and rigorous methods. They assisted this research in constructing in the multiple themes about the CFDI that emerged from and could be linked directly to the raw data. The text was analyzed at various levels, anywhere from the use of single words to sentences or whole paragraphs, and between transcripts, which allowed the researcher the freedom to be flexible, a characteristic of qualitative analysis. Being flexible allowed an unrestrained inductive analysis that helped the researcher understand the multiple perspectives of key informants and form an overall picture of the CFDI (Patton, 1980).

3.7 Defending against threats to analytic validity

There are processes defined by Huberman & Miles (1994) and Patton (2002) that assist the researcher in guarding against threats to the validity of the qualitative analysis. It is important to link the data with the findings in an observable and replicable way. To assist this process Huberman & Miles (1994) suggest the researcher "shift between cycles of inductive data collection and analysis to deductive

cycles of testing and verification" (p. 438). Attempts were made to verify such information pathways during the course of this study, such as described previously in the description of study design and data analysis. For example, themes were directly linked to the codes that composed them, and then codes were linked to their root quotations. This provided a way to verify and reinforce the development of codes and themes. Additionally, a second researcher was used during the beginning phase to determine rater reliability. More specifically, the second reader independently coded several transcripts and then the codes were compared for similarity and differences (reported in the results section).

Additionally, as suggested by Huberman & Miles (1994), techniques were kept in mind throughout the analysis to assist in verification, such as guarding against: data overload, salience of first impressions of data, overconfidence in a single piece of data or participant's response, the number of occurrences of data signaling meaning, and an over accommodation of the data that fit into the research objectives.

The next chapter will present the result of the research study and describe the themes which arose from the application of the previously described methodology. The sections of the next chapter are first divided by participant group then subdivided by each theme. Results of the within group analysis are provided first then the between group analysis is presented.

CHAPTER 4: RESULTS

4.1 PARTICIPANTS

Seventeen interviews were conducted in May and June 2009, eight with CFDI investigators, nurses and coordinators, four with patients, three with pharmaceutical industry representatives, and two with provincial government representatives. Due to unavailability for an interview, one questionnaire consisting of the research questions was completed by a patient representative. This resulted in a total of 18 participant interviews, eight more than the original proposal. The mean length of the interview was 38:05 (min: sec), with the shortest at 25:34 and the longest at 1:05:18.

4.2. CONTENT ANALYSIS

Analysis was performed using Atlas.ti for identification of codes, code families and data reduction. A total of 78 codes were identified during analysis. A second independent coder was used for two transcripts to determine inter-rater reliability using the formula ([total codes (102) – # of disagreements (17) / total codes (102)] x 100). The raters achieved an 83% agreement, which is appropriate as suggested in the literature (Cote et al., 2009). Codes were then used to identify 23 categories, which were reduced to 13 themes (nine within group, four between groups). Categories and themes were developed by the primary investigator. The within group themes were: 1) CFDI challenges, 2) positive characteristics of CFDI, 3) negative characteristics of CFDI, 4) model of orphan drug policy, 5) patient concerns, 6) primary objective, 7) origin of the CFDI, 8) government challenges, and 9) patient

objectives. The between group themes were: 1) the importance of the CFDI, 2) CFDI in stasis, 3) reimbursement problem solved with research, and 4) alternative policies. The results were analyzed separately for within-group and between groups.

4.3. WITHIN GROUP ANALYSIS: PATIENTS

A summary of the results of the within group thematic analysis of the patient group are shown in table 1. The patient category had four dominant themes that emerged during their interviews: 1) patient concerns, 2) negative characteristics of CFDI, 3) positive characteristics of CFDI, and 5) patient objectives. Overall, patients were happy they were receiving ERT, and if the CFDI was the only method of access that would have been okay. However, a source of discontent was that Canada has a public health-care system so patients felt they should not have been forced to participate in a research trial to receive a treatment that had been approved by Health Canada and is accessed in other countries. They also thought they should have had influence in their treatment options.

4.3.1 PATIENT CONCERNS

Patient concerns were highlighted by issues of information provided, consultation received, perceived challenges around outcomes/objectives of CFDI, ethical issues, and protocol of the CFDI. Patients were generally unsatisfied with the information they had received regarding the CFDI's methods, objectives and outcomes. Some patients reported receiving nothing from their physicians, for example Patient Respondent 3 (PR3) stated there has been some discussion but little information has been passed between the patients and the lead investigators. Other

patients, like PR1, were concerned, saying, "we are kind of in the dark.... the level of consultation with us is very low." Lack of understanding was a problem: "I don't think in general the patients really understand what is going on. To them they just think they are getting ERT, thank you very much (PR1)."

The lack of consultation has led to patients not understanding the justification behind the creation of the CFDI:

> "Originally the federal [and] provincial governments and pharmaceutical companies agreed to finance a temporary study in order to get information... But when we get the result that yes it is efficient... it already has been tested everywhere else in the world, so I don't know why it has to be tested again (PR4)."

A major concern was the restrictions of the CFDI protocol in terms of accessibility, inflexibility of protocol and treatment of the patient. The patients do not believe their health is of priority in the CFDI, saying, "The patient is really not coming first. The health of the patient is not first and foremost. What the CFDI is to me is research, research, research, and patients' health is secondary (PR3)." This is also reflected by the inflexibility of the protocol in regards to patient mobility to change treatments, as illustrated by a patient story:

> "At the last meeting, a family was sobbing because they felt the drug (being used) was ineffective but they had no option for dosage escalation or change. Patients who should be on therapy and would be if they were in other countries are being denied access under the guidelines of the CFDI. The natural history arm is a poor excuse for keeping patients out of treatment (PR2)."

The previous quotation is not used to indicate any negligence on the physicians' side but a frustration from the patient's perspective. The dosages cannot be changed based on Health Canada's report and as recommended by the treatment

providers. Doing so would violate the requirements for treatment passed down by Health Canada. Additionally, the opinion of the patient representative that patients should be on treatment is a lay opinion and not a medical perspective; however, it does demonstrate patients' confusion and frustration with the CFDI, potentially due to the lack of communication between groups.

Patients saw the CFDI as riddled with ethical problems, particularly regarding the guidelines for access which were considered too restrictive and out of date. Although the CFDI is an ethically approved research study, updated guidelines have not been implemented since 2005 (Clarke et al., 2005). This inability of the CFDI to update guidelines based on new information has frustrated patients and they consider it unethical. Furthermore, patients saw the existence of the natural cohort as unethical, saying: "We are asking this individual to sacrifice his health in order to collect data. I have a tough time with that (PR1)." Patients also viewed it as unethical to be forced into a research study in order to receive a treatment they viewed as effective: "I call it blackmail. I saw it as blackmail. Either you do it to you don't get the drug. So I didn't have a choice. That does not happen with any other medication if I am sick I get a medication (PR5)."

4.3.2 Negative characteristics of the CFDI

From the patients' perspective the negative characteristics of the CFDI have caused many of their concerns. Patients saw inflexibility of protocol, randomization, and outdated guidelines as negative characteristics of the CFDI. An inflexible protocol that did not allow for patient mobility between treatment groups was a major problem that stemmed from the fact that the CFDI is primarily a research study, not a

drug reimbursement program. The perspective that updated treatment guidelines have not been implemented in the CFDI, even though investigators recommended changes, was also seen as a weakness. Physicians' inability to address patient concerns was a negative quality. It was believed that, "there is no evidence that the researchers have advocated for a change to treatment guidelines (PR2)."

4.3.3 Positive characteristics

Positive characteristics of the CFDI were the national access to ERT, and the monitoring of patients. Patients were discontented with the guideline restrictions but were happy that the drug was being provided for them and their families, and they did see a role for guidelines to ensure those who did not need it would not receive treatment. The national scope of the CFDI, with patients being treated and monitored no matter where they lived, were characteristics patients deemed positive. Overall, patients thought the program was a model that provided access to a treatment that many patients in certain provinces would otherwise not receive. In that respect patients were satisfied.

4.3.4 Patient objectives

One patient (PR3) summarized what Fabry patients are looking for in terms of access to ERT:

> "We (the patients) have three key issues. One is the funding of ERT in the publicly funded health-care system. The next most important is what guidelines the patients have to meet to qualify for access to ERT. Our number three priority is ongoing monitoring, which is to a certain extent where the CFDI comes in (PR3)."

The three objectives stated in this quotation were echoed throughout the patient group. It was evident that patients did not want to be treated differently than other patients in Canada, and they felt that the CFDI was treating them differently. Patients also believed that enzyme replacement therapy was an effective treatment to reduce painful symptoms and help them and their families live constructive lives. Additional objectives were funding and monitoring on a nationwide basis, and flexible guidelines based on international standards.

4.4. Within-case analysis: CFDI investigators

A summary of the results of the within group thematic analysis of the CFDI investigator group are shown in table 2. Five themes emerged from the CFDI investigators: 1) origin of the CFDI, 2) primary objective, 3) positive characteristics of the CFDI, 4) negative characteristics of the CFDI, and 5) model for an orphan drug policy. Overall, CFDI investigators described the CFDI as a well organized, centralized program headed by specialized physicians who provide access to ERT while monitoring and recording patient progression on the treatment.

4.4.1 Origin of the CFDI

The origin of the CFDI dealt with the situation in Canada in regards to how expensive drugs for rare diseases were accessed before the CFDI, and how these factors were related to the driving force of the CFDI. For example, Investigator Representative 3 (IR3) stated,

> "...when (ERT for) Fabry disease came along it was quite clear that the governments were quite leery about paying this large amount of money [resultantly] patients were going off treatment...the companies gave up and said we were not going to give you any more

medication… Some patients in Canada actually died."

Another CFDI investigator stated, "The CFDI started off as an idea of a money laundering scheme and a way to get around the common drug review (IR2)." Only certain provinces had policies in place to deal with the rising cost of treatments for rare diseases, therefore the provincial and federal governments, "needed some kind of unique venue, it's almost an excuse, you know, the study part was an excuse to get the drug covered (IR5)." So, "essentially they tried to solve a reimbursement problem by designing a research study and funding the problem through that method, instead of just deciding to reimburse the drug (IR6)." There was particular concern for patients in Nova Scotia. Nova Scotia has the highest prevalence of Fabry patients, but was a province where patients stopped receiving ERT when the companies withdrew compassionate use. The origin of the CFDI is very important because it was a response to a reimbursement issue in the form of a research study, which has led to many of the problems from the perspective of the investigators, as well as the other groups (a theme that will be discussed in the between group analysis).

4.4.2 Primary Objective

From a CFDI investigator's perspective the primary objective of the CFDI was, "to get patients access to these drugs, once they were taken away" (referring to the treatment provider's removal of the drug for compassionate use) in a way that would "inform government as to whether they should reimburse these drugs or not, by developing long-term outcomes (IR4)." CFDI investigators individually agreed that patient access to ERT was of upmost importance during the development of the

CFDI and that a funding arrangement for a research study was the appropriate answer in 2005.

4.4.3 Positive characteristics of the CFDI

Database and ongoing monitoring, national coverage with a standardized approach, access to treatment, patient satisfaction, identification of new patients, and the independent scientific oversight committee were positive characteristics of the CFDI.

The ongoing monitoring and national database was viewed as the most positive aspects of the CFDI from an investigator's perspective, and was nearly always the first item mentioned when strengths of the project were discussed. "We have no reporting bias in our patient enrolment... we have basically enrolled all Canadian patients, whether or not they are on enzyme (IR4)." This allows for excellent follow-up and early access to ERT for patients who have been diagnosed but are not meeting inclusion criteria for treatment. It also allows for more information gathering on the progression of Fabry disease. Providing ERT to patients on a nationwide basis using standardized criteria was deemed a strength of the CFDI. Investigators saw this as a unique aspect in Canadian health care: "I think it's amazing... the way they (the provinces) are working on this is really unprecedented. Quite remarkable... (IR1)"

Access to drug where there is no other alternative was another positive characteristic of the CFDI. CFDI investigators believed this was the only option for the patients to receive ERT in Canada. Without it there would be piecemeal access and many provinces would not fund it. One of the investigator believed, "the CFDI is

a very efficient way of actually getting the drug out to patients (IR3)." As mentioned, the CFDI investigators were especially concerned about patients in Nova Scotia not being able to access the treatment due to cost.

From the perspective of CFDI investigators, patients were generally satisfied with the CFDI: "They were happy to have the CFDI in place to ensure that anybody who meets the guidelines regardless of where they live can get on the enzyme (IR7)." They believe it is a way for patients to get treatment by specialized doctors with excellent follow up and that makes them satisfied because they see ERT as a lifesaving drug.

As a national program the CFDI has been able to raise awareness of Fabry disease and the number of patients identified with Fabry disease has risen beyond expectations. Investigators believed a big part of the study was to increase the number of patients who are identified with Fabry disease and have them all in one database. These patients otherwise may not have been diagnosed with Fabry disease or may have gone unreported and untreated in some provinces.

The independent scientific oversight committee (ISOC) was viewed as having an important role in the CFDI by ensuring the database is composed of high quality data: "They have been extremely supportive of the study.... I think they've been a good set of eyes to look at data and to look at the overall study itself to point out some things (IR8)."

4.4.4 Negative characteristics of the CFDI

Negative characteristics of the CFDI as viewed by investigators are a lack of a single sponsor, funding issues, and heavy workload.

CFDI investigators saw many problems develop because the CFDI has too many different funding sponsors instead of having one body that would serve as an administrative sponsor. Currently any recommendations for changes in protocol or guidelines have to be approved by research ethics boards at each research site, by the ISOC, as well as by each province, the federal government and the two treatment providers. To the dismay of CFDI investigators, this results in a long, burdensome approval process that has resulted in no recommendations being implemented thus far.

Despite annual recommendations from investigators patients are still accepted based on the 2005 guidelines for access:

> "Somebody has to step up to the plate and say we are the sponsor for this project. We are tired, the doctors, I'm speaking on behalf of the doctors now, but it very frustrating not to be able to identify one person who is willing to represent all of the players, and is willing to take responsibility and make decisions about sponsor (IR4)."

Additionally:

> "There are five sub sites and five regional sites, that's 10. It could be a couple of years before we get paperwork approved. The study could be over. It's very cumbersome process (IR2)."

At the time of interviews, funding of the CFDI was to cease at the end of September 2009. However, funding has been continued since, but without any long-term commitments about the future of treatment or the CFDI. The thought of no long-term funding continues to be an issue that investigators would like to have dealt with when the study commenced because their outcome goals were designed to be accomplished in 10 years minimum. The funding was also not inclusive of all activities such as hospital infusion. "When we were given a budget to operate or to

put this protocol in place there was an oversight in that we weren't provided funds for patents to be infused in hospital (IR6)." Although funding is continuing at present (November 2009), long-term funding is still not guaranteed.

The heavy workload physicians, nurses and coordinators have had to deal with has resulted in everybody being, "stretched a bit too thin. I think we didn't realize the amount of work this would generate (IR8)." The lack of a single sponsor and no additional funding for problems or needed staff has also contributed to the additional workload: "It's also a colossal amount of work. As far as weaknesses, the actual amount of work it is taking to get this stuff together, and not just for the coordinators, but I have to say personally, for physicians (IR4)."

4.4.5 CFDI AS A MODEL FOR A NATIONAL ORPHAN DRUG POLICY

From the CFDI investigators' perspective, certain characteristics of the CFDI could be included in a national orphan drug policy in Canada, such as a national database with monitoring and guidelines for treatment. When asked whether the CFDI could be used as a model for a Canadian ODP, one participant stated:

> "It's nice to know long-term outcomes, so from an educated research point of view it's great to know that. We should know that for all our drugs, we don't have a venue for that, so I think my short answer is yes. It allows the drugs to get paid for. It allows a funding model that everyone has a stake in, the federal, provincial [governments] and the drug companies... and it then gives some long term data. You've got long-term safety data, outcomes, you know everyone is looking for outcome studies these days, so yes, it's something that would be beneficial (IR5)."

This quotation identifies important characteristics of the CFDI that could be replicated for a national ODP, such as outcomes, funding model, provincial collaboration, and pharmaceutical industry cooperation. However, there were

reservations about the need for extended funding agreements before an initiative like this would be replicated. Also, the depth of information needed for monitoring and the inclusion of a single administrative body to head the program were stipulations that CFDI investigators included for a national orphan drug policy similar to the CFDI.

4.5 Within-case analysis: provincial government representatives

A summary of the results of the within group thematic analysis of the provincial government group are shown in table 3. The within-case analysis for provincial government officials uncovered four themes: 1) lessons learned, 2) government challenges, 3) negative characteristics of the CFDI, and 4) positive characteristics of the CFDI. Overall, despite many problems with the CFDI, the provincial governments were satisfied with its creation and existence and have learned a lot of lessons from their experience.

4.5.1 Lessons learned

Lessons that were learned during the development of the CFDI and its maintenance included possible alternative methods for providing EDRD, and the potential for the CFDI to be used as an ODP. Provincial government representatives (GR) were satisfied that, "we get learning, we actually get to study it. We get real-life experience. We also get negative things (GR1)." The governments experienced how an interprovincial collaboration can and can not work. One participant believed:

> "From a program policy standard we ask how feasible it is to conduct a study within a public drug program. So this has been a great learning [experience]... It is something we can do, it costs a little bit, [we] know some of the long terms, (and) what is the time requirements to

> administer these programs. So it gives us a bit of perspective around what are the mechanics in place to successfully move these studies forward. So it's a good learning experience for everybody (GR2)."

As a model for a national orphan drug policy, government officials did see the CFDI as a starting point but not as the final answer. The possibility of a national policy was not reported as probable from the government officials because health care in Canada is a provincial jurisdiction, therefore provincial collaboration, along with industry negotiations, were viewed as too difficult.

4.5.2 Government Challenges

Provincial representatives were concerned about the challenges presented by having a research protocol as the basis for access because it sets expectations and brings up funding issues. One respondent stated, "the initiative [CFDI] is actually a representation of the challenges associated with drug programs across the country on a number of fronts (GR1)," including disease prevalence in different areas of the country, reimbursing EDRD, provincial collaboration and assessing clinical evidence for EDRD.

Provincial representatives did not want to provide a treatment that could harm their citizens, therefore they wanted a clinical study to demonstrate clinical effectiveness and cost effectiveness, thus the CFDI was supported. One participant stated when referring to ERT, "we have the challenge of equality. We agree that may be the only product, but does it work… so it's a challenge we have (GR2)." Provincial representatives, "want to be sure that by giving it to patients you are not creating harm. Just to say someone is worse off; it's hard to put that into context without saying what the clinical decisions were to support that process as well

(GR2)." The CFDI gathers this necessary information that was missing from the manufacturer's submission to the CDR. Representatives also saw an issue with using a research study as a basis for access, saying, "from a program perspective I am a bit cautious that we are bringing in so many restrictions that it becomes difficult to manage the funding of the product and it becomes difficult to get product to the patients (GR2)."

The provincial representative perceived a problem with linking research with government reimbursement because once the drug is made available it would be a major problem if the drug needed to be removed if the research suggests the drug is not effective: "Once you've given something it is extremely difficult to take it back... the research can advance the reimbursement decision right? But it often cannot reverse the access that's already been granted (GR1)."

Funding arrangements between the provinces was seen as a key challenge: "When you talk about shared funding it becomes a challenge. Who holds the money, where do you get it, who pays who? But it's not insurmountable... the jurisdictions are always strained with resources, so, simpler is always better for us (GR2)." Therefore the provinces view single province funding as a better solution, but a national policy is possible.

4.5.3 Negative characteristics of the CFDI

Although satisfied with the learning experience the government officials viewed the existence of the CFDI as problematic because it was a research study designed to solve a reimbursement issue: "A research study is a research study, accessing product is a reimbursement issue. They are different issues (GR1)." The

officials believed the CFDI will present a problem when funding is over because, as mentioned in the preceding section, "once you've given something it is extremely difficult to take it back (GR1)." Therefore, the CFDI presents the provincial governments with hard questions and will force them to make difficult decisions when the federal funding for the CFDI runs out. An alternative approach is to develop a consistent approach to reimbursement throughout Canada. Additionally, a negative characteristic was that provincial representatives believed patients' voices were not being heard and that their needs were not a priority in the CFDI. This was something the provincial governments recommended be changed in any future initiative.

4.5.4 Positive characteristics of the CFDI

Despite challenges and deficiencies, the provincial representatives described the existence of the CFDI as positive. Specifically, they detailed the national standardized coverage, a "core group of researchers (GR2)," establishment of a national database and ongoing monitoring as strengths of the CFDI. They believed these characteristics are aspects that should be included when moving forward with provincial initiatives or on a national approach.

4.6 Within-case analysis: pharmaceutical providers

A summary of the results of the within group thematic analysis of the pharmaceutical provider group are shown in table 4. The within-case analysis for the pharmaceutical providers revealed five themes: 1) CFDI challenges, 2) lessons learned, 3) the CFDI as model for national orphan drug policy, 3) positive characteristics of the CFDI, and 4) negative characteristics of the CFDI. The

treatment providers were satisfied with the arrangements made when the CFDI was initiated, however, they see the inability of the CFDI to change its protocol/outcomes based on new information and to keep up with what is being done internationally as major drawbacks. This stems from the fact that it is, above all things, a research study.

4.6.1 CFDI CHALLENGES

Challenges that face the CFDI are: statistical problems in terms of achieving its outcome goals, its relevance to global research, sponsorship, and the state of the Canadian health-care system. Pharmaceutical representatives do not believe that the CFDI can reach its outcome goals in terms of comparing the two drugs, for example one industry representative (DR1) stated, "maybe people will hope time will go on forever and eventually if you have a long enough randomization you may come up with an answer, but an underpowered study is a self fulfilling prophecy to repeat the claim there is no difference [between the two treatments]." It must be reiterated that this and other quotations are how the group perceived the CFDI from its position.

Pharmaceutical representatives could not comment on the depth of the database, but they were certain that the CFDI will not have a major contribution to the international research community in terms of providing new evidence: "One of the fundamental questions is whether or not the Canadian database is going to add any (thing) additional to what is being monitored, looked at internationally, with a much greater number of patients (DR3)."

The inability of the CFDI to implement guideline changes or incorporate new information based on international research data was seen as a major challenge. This

was attributed to a lack of a head sponsor: "The world has changed; it's like building an airplane while you fly it (DR1)." Related to this is the state of the health-care system in Canada: "It's a difficult situation because the Canadian health-care system is in shambles. I studied it for years. It doesn't work. Nobody wants to hold the ball (DR2)." This refers to health care being a provincial jurisdiction and not being uniform across the nation.

4.6.2 Lessons Learned

Lessons that can be learned from the CFDI are that ongoing monitoring, and collecting of data are very important components of a rare disease treatment reimbursement policy. Pharmacy representatives did believe the system the CFDI has in place can work, however, access should not be dependent upon participation: "What you are asking is whether or not having access to therapy and having the CFDI are two separate things. I believe they should be separated (DR3)."

4.6.3 CFDI as a Model for a National Orphan Drug Policy

The pharmaceutical providers think the CFDI is a flawed model: "In a situation where you are doomed to fail is it ethical? No. Is it a good model? No (DR1)." therefore they do not believe it would be a good model for Canada to use as a national program for accessing EDRD:

> "I would say no, it's not a good model. Principally because it is fixing a problem but there's a better way to fix this problem and that problem is just to have a national rare disease policy and right up front make some commitments about achieving global standards in the treatment of people with rare disease and follow that policy. Don't make up clinical trials that are really meant to solve a reimbursement issue. If you need to do research, do research. If you need to reimburse,

reimburse. But don't use research to solve the reimbursement question (DR2)."

4.6.4 Positive characteristics of the CDFI

Keeping a national database, monitoring patients and access on a national platform are the positive aspects of the CFDI. Without the CFDI the treatments would not be accessible for many Canadians with Fabry disease. The pharmaceutical representatives acknowledged this but did not consider the CFDI as the best program to accomplish this goal.

4.6.5Negative characteristics of the CFDI

The CFDI's foundation as a research study was reported as the major weakness because it randomizes treatment and it is in a form of stasis in regards to protocol changes. This is partly because, "there is nobody who wants to do it, because it's the wrong design, the wrong setup to get someone to be a sponsor for his study (DR1)." According to the treatment providers, the CFDI does not have the statistical power to answer its outcome goals or provide new information to the international community within the three years of funding. However, reports by the ISOC do indicate that the CFDI will be able to meet the outcome goals if they are allowed to continue on their original 10-year plan.

The pharmaceutical representatives believed that the CFDI's inclusion criteria were too strict and outdated. There was great criticism toward the CFDI because of its, "inability to treat all Fabry patients or there's an inability to treat Fabry patients, who are suffering from the disease with symptoms that would be treated in other

countries, but because of the extremely strict criteria that are dated [they are not treated] (DR2)."

4.7 Between group analysis

A summary of the results of the between groups thematic analysis is shown in table 5. A between group analysis was conducted to find themes, "that cut across cases" (Huberman & Miles, 1994, p. 436) and identify key patterns to clarify the overall effectiveness of the CFDI from the perspectives of the various stakeholders. There were many differences between groups as revealed in the within case analysis, however, specific themes did emerge from the data when all groups were considered. The analysis revealed four themes that were present in all groups: 1) importance of the CFDI, 2) CFDI in stasis, 3) reimbursement problem solved with research, and 4) alternative policies. Overall no party was completely satisfied with the CFDI's design. Nonetheless, there were certain aspects of it that were considered important and beneficial if used in a Canadian orphan drug policy.

4.7.1 Importance of the CFDI

National access to treatment based on standardized criteria, administered by a core group of specialized physicians who conduct ongoing monitoring and establish a national database was reported as a vital feature of the CFDI. According to participants, this feature would also play an important role in a national orphan drug policy. Of significant importance is that the CFDI was a method that successfully got patients with Fabry disease on enzyme replacement therapy, despite apparent weaknesses in structure. Many patients across Canada, specifically in Nova Scotia,

would not have received the treatment without the CFDI. Additionally, awareness of Fabry disease would not be as high.

4.7.2 CFDI IN STASIS

The major problem that all groups had with the CFDI is that it has not updated its protocol or guidelines in the nearly three years it has been in existence, despite investigator and ISOC recommendations and patient concerns. This has been attributed to the resources available and the multitude of parties involved in its administration, such as the physicians, the provincial governments, the pharmaceutical providers, and the ISOC. One participant stated, "Any modifications to protocol, any reports, anything that has to be done, needs to be cleared by all the stake holders before it can be considered cleared (IR1)." Another participant reiterated the concern: "It could be a couple of years before we get paperwork approved. The study could be over. It's a very cumbersome process (IR2)." To the frustration of all parties this means that the criteria for treatment has not been updated to reflect new information gathered: "The protocol was written in 2005 and it's now 2009, a lot more has been learned globally about the symptoms and treatment of Fabry disease, and none of those global learnings have been incorporated... [referring to CFDI guidelines] (DR2)." Physicians have annually updated guidelines for treatment based on new information, but have been unable to get sponsors to agree to implement the changes into the CFDI. One pharmaceutical representative stated that he/she had just recently received the recommendations within the past weeks before the interview. This would be two years after the recommendations were originally suggested.

Additionally, the physicians are overburdened with work to treat patients and collect data as well as run their own practice outside of the CFDI: "I think you have to look at the five physicians on the scientific committee (who) also have huge practices that they deal with and I think the downfall that way is that they didn't realize the work that this is generating. I think that's one of the downfalls (IR8)." These two components combined with the underlying research design of the CFDI inhibit any modifications that have been suggested by the affected parties, such as implementing new treatment guidelines, and removing randomization to treatment groups.

4.7.3 Reimbursement problem solved with research

In addition to the problems surrounding implementing changes to the CFDI, there are problems with treating patients under a publicly funded study. "Essentially, they tried to solve a reimbursement problem by designing a research study and funding the problem through that method, instead of just deciding to reimburse the drug (DR2)." This has created great ethical concerns for the parties involved, and made patients feel forced into the trial to receive their treatment: "I think it's totally inappropriate that Canadian Fabry patients who want access to ERT through the publicly funded health-care system are forced to become a member or register for the CFDI. I think that's totally inappropriate (PR3)." It was also viewed as coercion and blackmail by some respondents.

Due to the underlying design of the CFDI as a study, it has an inflexible protocol for changing treatment regimes or doses: "The fact that patients must be randomized to one of the two drugs is a major weakness, as well as the fact that they cannot change treatments, if the one they are on is not working (PR2)."

4.7.4 ALTERNATIVE POLICIES

Throughout participant interviews, solutions to the CFDI were mentioned. Many respondents referred to what other countries are doing to promote access. The United Kingdom policies were mentioned as possibilities frequently, for example, "The approach used by the UK in their Rare Disease Commissioning approach (where patients are put on individual treatment contracts and continuance) is based on achieving desired benchmarks (PR2)." Additionally the Netherlands was praised for its policies that "provide for individual protocols, including early entry to treatment, dosage manipulation, and additional follow up. Most other countries have international guidelines that are based on the latest data (PR2)."

Simpler solutions were also recommended such as disregarding the research outcomes and the research protocol and instead administering guidelines, monitoring treatment progression and submitting data to international databases. This would be similar to what is being done with Gaucher's disease. Essentially participants wanted the federal government to take the lead and, "kick start issues around making changes to help Canada's policy of reviewing and approving a drug for rare disorders (PR3)."

CHAPTER 5: DISCUSSION

5.1 ANSWERING THE RESEARCH QUESTIONS

The ultimate purpose of an evaluation is to provide novel information for decision makers and information seekers about the program (Patton, 2002). This evaluation discovered various aspects of the CFDI that could only be revealed via in-depth interviews with various key informants. Therefore, this study was successful at using an inductive approach to content analysis to produce novel information that developed a holistic perspective of the CFDI. Thirteen key themes were revealed during the evaluation of the CFDI. The underlying meaning of these themes can be used to educate decision makers on how to improve the CFDI in its current state, and help program developers identify elements to include or avoid for future initiatives of this sort.

In this discussion chapter, the themes will be interpreted through the original research questions proposed for the study, which were: (1) assess whether key informants perceive that the CFDI is meeting its goals and objectives; (2) determine if the key informants believe the CFDI is a model that can be applied to other treatments for rare diseases; (3) provide recommendations, developed from variety of perspectives, that could improve the CFDI; (4) gather perspectives as to whether the ISOC is contributing to or detracting from the CFDI; and (5) understand whether the key informants believe resources given were appropriate for the study. Through the course of data collection and analysis the researcher was able to answer these questions and provide additional information that emerged through the research

process. This discussion will answer each of the research questions, describe the impact of the findings and link the findings to known literature.

5.2 Assess whether key informants perceive that the CFDI is meeting its goals and objectives

The five main goals of the CFDI were primarily designed to be information-gathering goals about the impact of ERT on complications of Fabry disease and identify how to best predict ERT outcomes and side effects. The CFDI has been collecting data to reach these goals but there have been delays in inputting and analyzing the data. The delay has been because of funding and sponsorship issues that have existed since the inception of the program. Post analysis, the researcher attended an August 14th Post 3-Yr CFDI Fabry meeting regarding the continuation of the CFDI and patient access to ERT. Present at that meeting were members from the patient, CFDI investigator, provincial and pharmaceutical representative groups (not specifically those who were interviewed). During that meeting Dr. Daniel Bichet, a CFDI investigator, presented findings thus far from one regional site (Dr. Bichet, personal communication, August 14, 2009). The presentation described the large amount of information that is being gathered in the CFDI and how it is being used to help identify new patients with Fabry disease through genetics and diagnosis. There was also a significant amount of information regarding the complexities of Fabry disease that has been uncovered through the CFDI. It was obvious that the investigator was satisfied with the data gathering efforts of the CFDI and the attendees were impressed by the depth of information.

The CFDI is currently trying to meet data gathering outcome goals, but there was a great deal of skepticism among participants about whether the CFDI's outcome

goals could ever have a significant impact on Fabry research worldwide. This view point was a dominant issue throughout analysis, despite recent evidence that the CFDI is gaining international attention. For example, recently there were two poster abstracts related to the CFDI accepted at the 9th Annual European Round Table on Fabry Disease (Weidermann, & Breunig, 2009). Although the CFDI has had setbacks in input and analysis, the data being gathered is of great use to the researchers and patients because they are discovering more and more about the benefits of ERT and the complications of Fabry disease. It is a resigned perspective to believe this information will have no benefit. This viewpoint may have arisen because of frustration with the CFDI and its inability to implement updated protocol and guideline changes. The CFDI has the largest enrollment of patients in a single study, and it is gathering data on a variety of outcomes including biological markers (i.e., kidney, heart, gastrointestinal pain, chronic pain & quality of life questionnaires), therefore the CFDI could have a significant contribution, beyond industry registries, to international knowledge of Fabry disease and ERT.

It is evident that the CFDI will not meet the sixth goal of comparing the two drugs unless funding is provided for at least 10 years. This fact is supported by the 2nd annual report and research update for 2007-2008 (Hollak, et al., 2009). The report details that the CFDI still has had delays in patient testing, data entry and analysis. Although there are 259 patients in the CFDI, only 14 patients have been analyzed for differences in treatments. Subsequently no difference has been detected between the two. The CFDI investigators report that their biostatistician calculates it will take 80 patients or more to meet their outcome goal of comparing the two drugs, if there is a real difference. It will take 10 years to enroll 80 patients but they do not know how

long the patients will need to be on treatment to accomplish that goal. This information was reported a mere three months before funding was scheduled to cease. With this information it is clear that the CFDI is not well designed to accomplish their outcome goal of comparing the two drugs within their stated timeframe, especially without secured funding. This supports the opinion of many participants, including CFDI investigators.

Of the other five outcome goals only one has been reached thus far, the establishment of a nationwide registry to collect information on all persons with Fabry disease. The information is required to be inputted for every patient at each site; however, the 2006-2007 ISOC report and the more recent CFDI report noted delays in inputting outcome data. This may be due to the heavy workload and lack of staff stated by the CFDI investigators. With the inclusion of additional resources into the CFDI or earlier access to the funds this may have been avoided. Additionally, the CFDI lead physicians are not being remunerated for their work with the CFDI and they do have other clinics to operate. However, they did report that they were doing a good job gathering data and that their database will be the largest and most unbiased. This is a learning experience for the CFDI: establish the funding arrangements and budget allocation before the initiative is expected to produce findings.

The question remains of whether the data will ever be inputted if funding is not secured. Currently, B.C., Alberta, Quebec and Ontario have agreed to continue funding and Nova Scotia has stated it will continue for another year, but will these provinces continue to fund the study for the minimum of seven more years? During the August 14, 2009 Fabry meeting, Ontario provided a letter of promise to the Fabry patients that the province would continue providing ERT to patients after October 1,

2009. Since then the Nova Scotia, Ontario and Quebec government have agreed to continue to fund the CFDI for an undetermined amount of time. If treatment is not continued long term, the situation from 2005 will reoccur and the arguments of patients and pharmaceutical representatives that the CFDI data would not contribute to the findings of international databases may be true. If funding for ERT but not the CFDI is provided, then the CFDI, as a research study, must be considered a failure.

The relevance of collecting data is not questioned, however, is it restricting access? Nearly all participants stated they believed collecting data was very important because the available information on Fabry disease and ERT is lesser when compared to more common diseases and their respective treatments. In 2006, a systematic review of the clinical effectiveness showed that ERT was beneficial for Fabry disease on several measures of pain, cardiovascular function and some end-points reflecting neurosensory function (Connock, Frew, Mans, Dretzke, Fry-Smith & Moore, 2006). However, the authors suggested that more information is needed before a general consensus of effectiveness can be reached. This information supports the CFDI investigators' beliefs that ERT needed additional clinical evidence to demonstrate effectiveness and rebuts the comments of the patients and pharmaceutical providers.

The results of the current study raise the question: why is there so much doubt towards the CFDI and its ability to reach its outcome goals? From a patient perspective, the lack of communication between CFDI investigators and patients may be the cause. More patient involvement and increased patient responsibility in attending physician meetings may increase optimism and activity regarding the CFDI. Having published only one update over nearly three years of operation has bred skepticism among the patient and pharmaceutical group. They believe the CFDI

investigators are not putting the patient first; instead, they view the investigators as putting a priority on research and not patient care. Since patients believe they are not getting the same level of care that they would receive in other countries, where access to ERT doesn't require participation in a study, they have begun to question the relevance of the CFDI and its outcome goals. More communication about the origin, purpose and current state of the CFDI may solve this problem. CFDI investigators, particularly the lead physicians, have dedicated their professional lives to lysostomal storage disorders including Fabry disease, and there is no doubt that the CFDI investigators are doing their best to provide ERT to patients while abiding by the CFDI study design. What they can do better is provide the patients with more support to deal with their frustration and concerns. Informed patients will be happier patients, even if the news is not optimistic.

5.3. Determine if the key informants believe the CFDI is a model that can be applied to other treatments for rare diseases

There was a mix of responses when presented with the question of the CFDI being applied to other treatments for rare diseases as a model for Canada to follow. Most agreed that the CFDI in its present form would not be a good model to follow because it is a publicly funded research study. However, there were certain characteristics of the CFDI all groups agreed could be used for an orphan drug policy. The characteristics are summarized in Table 6.

According to participants, an ODP in Canada must provide equal treatment access throughout Canada with inclusion criteria, data collection and ongoing monitoring, with a high level of care and that is outside the jurisdiction of the CDR. Participants saw that the characteristic of the CFDI that should not be transferred to

other areas of an ODP is the research study component which includes characteristics such as randomization, inflexible protocol and patients having to consent in order to get access to treatment. Participants believed characteristics that should be added are patient involvement in choices for treatment, voluntary patient enrollment in data collection without the consequence of treatment removal for not participating, and a single person or organization in charge of updating and maintaining the program's long-term funding arrangements. Also, patients' voices should be incorporated into the decision-making aspect of a policy, and something similar to the European Union's citizen council was suggested. In the EU, a panel of 30 citizens gathers on a weekend to discuss relevant health issues. At the end of the discussion there is a vote on how to proceed on the particular initiative; majority wins. The ten longest serving members leave every year, and ten new members join. This process is possible in Canada and could help patients become more responsible for health-related decisions. It may also increase faith in programs like the CFDI. This would be a valuable venue for patients to voice concerns in Canada, especially with unique initiatives like the CFDI.

The underlying negative factor of the CFDI is the fact that it is a clinical study creating too many restrictions for patient access. Guidelines, based on well-researched evidence-based medicine are a necessity too; however, the CFDI has failed to implement its updated guidelines based on new information that is available. The practicality of an orphan drug policy with discussed characteristics is unknown. Groups reported that the process of negotiating the CFDI was very difficult and time consuming, and that no group thought it was realistic that such a large-scale initiative would be engaged in again.

To further examine this question the researcher looked at elements of the CFDI that can be found in other international policies for EDRD. The policies of the United States, United Kingdom, European Union, Japan and Australia were reviewed in Chapter 2, Section 6. The researcher compared those characteristics to the CFDI to determine which policies and initiatives were found in both. The characteristics the CFDI has, which other countries have implemented, are that it provides financial support for researching the treatment, has a special approval process for the treatment, and is a national program. The specific details of the support are unknown, however, some participants believed it to be a 1/3 split between pharmaceutical providers, federal government and provincial governments. It was believed by many participants that duplicating this sort of cost-sharing arrangement would not be probable. However, the existence of negotiating principles for price and profit control in other countries encourages the future use of another type of arrangement.

The CFDI does not possess many characteristics that are found in international orphan drug policies designed to promote EDRD such as tax cuts, market exclusivity, priority review, control of profit margins, protocol assistance from government, patient representation, and support in the clinical trial phase. As a research study the CFDI was not designed to encourage such policies, however, the federal and provincial governments would be well served to incorporate such characteristics into future policies regarding EDRD. By doing, so the country would be adopting international principles that are well accepted in their respective countries and have been successful in providing EDRD to their citizens in an affordable manner.

Overall, a future Canadian program implemented to provide access of treatment to patients while monitoring them and recording data should be designed to

be more similar to a registry study instead of a research trial. Patients and pharmaceutical providers did not believe this model was a good one principally because it was "a bureaucratic solution to a reimbursement problem" which caused too many administration problems that resulted in an inability to put the patient first and to adjust to internationally available information. The CFDI investigators and the provincial representatives had a qualified yes to the question of the CFDI being a model for an ODP. Investigators saw it as a good tool to provide access to pharmaceuticals and to gather information for future decisions. Nevertheless, a stabilized structure for administration and funding needs to be established before it begins. Provincial government representatives did think that the CFDI had some characteristics that should be used in provincial policies but that a national policy was unlikely because of the difficulty in negotiating cost-sharing agreements between provinces and manufacturers. If these problems, however, were solved in a simple manner then they would be interested in such an arrangement.

5.4 Provide recommendations, developed from a variety of perspectives, that could improve the CFDI

Essential recommendations that would improve the CFDI are to have a long-term funding agreement, a single sponsor to administer recommended changes, and additional resources to reduce the workload on the physicians, nurses and coordinators. Additional resources could be used to establish a separate body that would be in charge of administering treatment or inputting data. Because the physicians in the CFDI are "only one line thick," if any one of them is no longer to continue in their respective area then it could be very difficult to provide a replacement and treatment may not go on without one. Therefore, establishing a

strategy around this possibility would be beneficial. This would require using the current CFDI infrastructure to develop an independent administrative body that could use the existing framework to continue the research. This would relieve the current investigators of a significant amount of work and create a separate body of specialists.

Randomized control trials are the benchmark for clinical trials. As such it would be extremely difficult to adjust the protocol of the CFDI without it losing its status as a clinical trial or compromising its goals. It is for this reason that a patient does not have an option to change treatments. Therefore, the only recommendation that would be appropriate is to drop the status as a clinical trial, but then the question of the funding arrangements is raised. There is a dilemma here, and the CFDI is stuck in its roots for now. If another initiative was created it should not be designed as a clinical trial but instead have access as the number one priority and research as a benefit.

The main question proposed by this study's results is whether a research study should have been designed or would a registry study have been sufficient? In 2005, when data on ERT was less available, a uniquely Canadian research study seemed appropriate given the amount of Fabry patients in Canada. Retrospectively, and for future consideration, a registry study may have been more appropriate. A registry study is less expensive because it is not as administratively heavy as clinical studies. Although registry studies do not produce the same quality data as clinical studies, because there is less control in a registry study, the data is still very valuable. Registries by the Canadian Cancer Registry, Gaucher's registry, Hemophilia registry and the Cystic Fibrosis Disease Registry provide examples of effective models to replicate for data gathering. The Canadian Cancer registry is a collaborative effort

between provinces to collect information gathered from all provincial registries that then combines them into one in order to better describe the diseases and their treatments. This may be an effective model to gather information on Fabry disease that would cost less and would not have as strict controls and randomization of treatment. However, the funding still needs to be secured for treatment. This is an issue that no participant knew much about, because the details of the negotiations between the parties were never published.

The recommendations above are similar to recommendations by Clarke (2006) who suggested that the CDR be redesigned to better accommodate EDRD. Included in his strategy was a commitment, primarily funded by industry, to ongoing monitoring of patients on the treatment through a registry study. Physician reporting to the registry would be a requisite for access. Furthermore, Clarke suggested that the registry be maintained by rare disease expert committees comprised of internal and external reviewers from a variety of health disciplines. The CFDI lead investigators could be perceived as a similar body. The data gathered from the registry would help make better evaluation decisions. Establishment of such a registry would provide benefits of the CFDI, such as patient access, monitoring and funding, while removing strict clinical trial protocol, such as randomization of treatment. These recommendations could use the infrastructure of the CFDI as the registry and the existing CDR as a method of evaluation.

5.5 Gather perspectives as to whether the ISOC is contributing to or detracting from the CFDI

With the exception of its absence during the first year of the study and forcing changes that were not welcome by the investigators, the ISOC has done its specified

job of reviewing and criticizing the data and procedures of the CFDI. Many investigators believe they have been very fair in their assessments. The problem is that the ISOC suggestions do not get implemented because of lack of resources and a single lead sponsor. Other than the CFDI investigators the other group members had no interaction with the ISOC and therefore had no opinion on its effectiveness. The ISOC and members of the CIHR declined to participate in the study; therefore, it is difficult to determine their effectiveness or the effectiveness of the CFDI from their perspective. There exists suspicion that the ISOC is not as independent as it claims to be because it has not forced recommendations to be implemented into the study.

5.6 UNDERSTAND WHETHER THE KEY INFORMANTS BELIEVE RESOURCES GIVEN ARE APPROPRIATE FOR THE STUDY

The funding for the CDFI has been appropriately distributed according to parties involved. There has been no misuse of money or misappropriation of funds. In the draft of the update it was estimated that the total cost of running the CFDI was approximately $800,000 per year, or only 1% of total cost of ERT which is $18 million a year across Canada. Additional funding would have been useful to employ more nurses, coordinators or administrative help, which could have helped implementation of recommended changes, such as funds to administer ERT in hospitals. The investigators have additional roles outside of the CFDI, and physicians have their own clinics to run, therefore they have limited time to do the paperwork necessary to force some of the issues they would like to and have recommended changes implemented in the CFDI. Therefore, although the funding was appropriate, there was no allowance for additional costs or problems that arose.

5.7 LIMITATIONS OF STUDY

Unfortunately, no ISOC or federal government representative agreed to participate in the study. All ISOC members, the CIHR and every province's department of health were contacted. Reasons cited for the ISOC were: timing issues, concerns regarding ISOC member's individual responses contradicting the committee's published findings, and conflict of interest. The timing issues were related to the publication of the ISOC's report which was expected to be published in July 2009, but was not published until the fall of 2009 (Hollak et al., 2009). The only response from the federal government was a referral of the request to another province. That province responded that it could not comment because it had no patients enrolled in the CFDI. Therefore, no federal government input could be included in the evaluation. Many provinces cited lack of knowledge about the CFDI or conflict of interest as reasons for not participating. Some provinces did not respond to several attempts to recruit.

Recruitment for the provincial and pharmaceutical representatives stopped when no more participants could be recruited after several months of attempts. Recruitment for CFDI investigators and patients stopped when adequate data had been collected and new information was not being presented from the latest interviews (Morse, 1994).

The absence of federal government officials, ISOC, and CIHR members participating in the present study has limited the perspectives available for analysis. The richness of the data would have been increased, however, it is not considered a significant detriment to the study. The study participants had extensive experiences

not only with the CFDI but also with the Canadian health-care system before the CFDI's creation and before the development of ERT; therefore, their responses were adequate to perform an evaluation of the CFDI.

The reluctance of government officials and pharmaceutical representatives to discuss the details of the cost-sharing negotiations also limits the evaluation. The negotiations concerning the cost-sharing relationship between the government and treatment providers that took place before the CFDI began is an important aspect to understand. If future initiatives are to happen it would be useful to determine the barriers that occurred during the lengthy negotiations. This would help identify how to more speedily overcome or avoid such barriers in the future. Additionally, facilitators of the process could be identified and replicated in future negotiations.

5.8 Ethical Concerns

From a clinical trial perspective the CFDI has gotten approval from the CIHR, and five local research ethic boards, therefore there are no apparent ethical concerns with the operations of the study. However, the concerns raised by patients, investigators, pharmaceutical providers and the government officials require that ethics be discussed. Although the CFDI was designed as a clinical trial, the driving force behind it was to get patients access to what was perceived by patients and investigators as a life-saving treatment. The only perceivable way to do this at the time was to create the CFDI, a randomized control trial. If the purpose of the CFDI was to get patients access and not research, the question becomes: Is research an ethical response to such a dilemma? Additionally, are the investigators unbiased

towards which treatment may be more effective or suitable to their patients (who are now participants)?

According to patients the answer is no, it is not ethical to conduct a randomized clinical trial as a response to a reimbursement problem. Government officials thought it was appropriate at the time but now see that there are too many restrictions causing problems with patient access. CFDI investigators believe that research was the only option due to the lack of data available at the time. CFDI investigators also believed that the treatments were effective.

With these points in mind, one may ask is a randomized trial ethical when the researchers may have a good idea that the treatment may work; even if has not been clinically proven. If so, it can be argued that the researchers do not have equipoise and cannot conduct a randomized trial ethically (Lilford, 2003). Additionally, the patients know which treatment they are being administered and as mentioned in the results, and have preferences to which treatment they may want. Is it ethical to keep a patient (or participant) on a treatment if they do not have equipoise? These are important questions for future research into the ethics of initiative like the CFDI.

Several more questions are raised when considering the previous question. For example, research in Canada requires voluntary consent and withdrawal, but do the patients really have free consent and withdrawal if doing so means that they will not have access to a treatment they perceive as life saving? Additionally, why aren't patients part of the decision-making process for which treatment they receive? There are large differences in the time it takes to infuse ERT; therefore, one treatment may be more suitable to the patient's lifestyle than another. These questions require answers before future initiatives such as the CFDI are undertaken.

5.9 INTERNAL AND EXTERNAL VALIDITY

Internal validity refers to the confidence that the research has been conducted in a way that minimizes or eliminates biases in data analysis and reporting (Moher, Jadad, Nichol, Penman Tugwell, & Walsh, 1995). As detailed in the methods, interview transcripts were repeatedly read and compared within and among groups by a researcher with no previous bias toward or against any group. All results were supported by use of quotations from the appropriate group. No theme or statement was presented without sufficient supporting material. Additionally, participants within groups reported similar knowledge, beliefs and opinions and there were few opposing responses. Between groups there were opposing responses and these were reported.

External validity refers to the degree that the results accurately reflect the expected responses of the remaining target population or how well the sample population's responses would fit into the target population (Leviton, 2001). Good external validity means that the results are an accurate reflection of reality. In this study the external validity is strong for the CFDI investigators and pharmaceutical providers. A majority of CFDI investigators were interviewed, including four or five primary physicians, and many coordinators.

It is more difficult to determine the external validity of the results from the patient and government representatives. Patients involved in the study often expressed opinions and beliefs they had heard from others. However, because all participating patients were involved in advocacy and the Canadian Fabry Association, it is difficult to determine whether their responses would be similar to patients who are less active

in advocacy. Additionally, no patients who were taken off ERT for a period of time were interviewed. Those patients may have expressed different experiences and beliefs about the CFDI.

Only two government officials participated in the study. It is hard to determine if their responses would be echoed by the other provinces, specifically provinces that had patients taken off the treatment or who could not afford to provide ERT to their citizens. All other provinces refused to participate despite several invitations. More participation would have provided a better sense of external validity.

Overall, this research made attempts throughout the development and conduct of the research to ensure that all steps were reproducible and results were supported by quotes. Therefore good internal validity is supported. The results of CFDI investigators and pharmaceutical providers will reflect their greater populations; however, the patient and government groups may be less general. Recruitment efforts were made to contact more individuals in both groups. The next chapter describes the author's conclusion from the research, directions for future research and the potential application of this research in the field health services.

CHAPTER 6: CONCLUSION

6.1 Conclusion

The CFDI is a clinical research trial, and is itself a prototype model of cost sharing, linking research to reimbursement and access to an expensive drug for a rare disease. However, as a model it has not met the needs of many groups that have a stake in it. No group was completely satisfied with the CFDI, primarily because it has two major weaknesses: there is no long-term funding to reach outcome goals, and the lack of a single head sponsor or administrative body for implementing modifications. This has resulted in it not ensuring its primary objective of providing access to ERT for patients with Fabry disease, at least on a long-term basis, and an inability to adjust to adversity or implement recommendations from investigators and the ISOC committee. However, the CFDI has been effective in providing drugs to patients on a nationally standardized basis, in the absence of any Canadian alternative, with a high standard of care using specialized physicians, while monitoring and recording the progress of Fabry disease and the effectiveness of two forms of enzyme replacement therapy. In regards to these aspects, the CFDI has done an effective job, however, when compared to international criteria for access there are patients in Canada not receiving treatment that would be given to them in other countries. Although the difference in inclusion is small, the existence of a difference has led to patient and pharmaceutical company concerns with the CFDI. Patients do not understand why the CFDI cannot change its criteria to keep up with what other countries, such as the EU,

are doing, and this has created frustration with the CFDI. Pharmaceutical providers believe in their product and want it to be accessible to as many patients as possible; therefore, they want the criteria to be as inclusive as possible.

The argument has been made that the number of patients not being treated is small; however, the number of patients affected by Fabry disease is also small. Furthermore, because Fabry disease is genetic, many patients have family members that are not on treatment. Therefore patients' concerns are understandable. The solution to remedy this on a national basis has escaped Canada for many years, and the lack of any progress in the National Pharmaceuticals Strategy indicates that any national policy is far off.

There are characteristics of the CFDI that would be useful and effective to incorporate into a national orphan drug policy that all provinces have an investment in, including: national patient access, a national database, ongoing monitoring, and treatment guidelines. Additional aspects that would be needed are long-term funding arrangements, a lead investigator or head sponsor, and ongoing patient consultation.

As a program that provides access to an expensive treatment and serves as a means to monitor and record data on a national basis, the CFDI is effective. As a program that could provide EDRD to patients in the future, it would need some foundational restructuring, therefore in its present form the CFDI would not be an effective model to use as a Canadian orphan drug program. The reason is due to the serious deficiencies in the CFDI, many of which stem from the foundation of the program being a clinical study. The design has resulted in excessive administrative duties entailed in implementing recommendations for guidelines and protocol. This is partly due to the fact that any changes must be approved by all research centers'

ethics review boards, and the CIHR's ISOC, but also because there is no one lead sponsor to implement changes nationally.

6.2 Implications for Health Services Research

Program evaluations can serve as useful educational tools for program stakeholders as well as policy developers. Although focused on qualitative measures and one program, the current evaluation of the CFDI can be applied by the various key informant groups used in it as an information source to advocate for improvement of the CFDI. Application of the various positive and negative characteristics identified and the suggested alternatives for implementation would prove useful. It can also be a resource for policy and program evaluators. Such information seekers and users can apply the results and learn of the benefits of this approach proactively to develop futures initiatives. This evaluation identified various barriers that are encountered when implementing a program within a publicly funded system, involving a vulnerable population in a treatment based program, developing programs with industry support and government involvement. It also addresses the limitations of Independent oversight committees and funding agencies as bodies of change and leadership, respectively..

6.3 Future directions

At the August 14, 2009 Post 3yr CFDI meeting, the principles for access to ERT for Fabry patients in Canada were discussed by members of the key informant groups. The outcome of the discussion included various aspects of the CFDI such as

equal national access, comprehensive care from centers of excellence (the five regional sites), and ongoing monitoring and care. There were also principles that were uncovered through this evaluation such as patient involvement in treatment options, patient education, and long-term funding arrangements without interruption of treatment, flexible guidelines, and a process to keep guidelines current. Additionally, the elimination of the natural history cohort was discussed and in its place a future program should provide preventative maintenance so that patients will not have to get sick in order to get treatment. These components were agreed upon by representatives from the four key informant groups and should be considered critical components of a future program in Canada. Furthermore, a major outcome of the August 14, 2009 meeting was that the groups agreed that research should continue but the CFDI needs to be redesigned. This is a similar finding to the present research and supports the conclusion from this evaluation.

The CFDI does provide hope for future interprovincial collaboration efforts and demonstrates that expensive drugs for rare diseases can be treated and monitored cost effectively. It has also been a valuable learning experience for government, the pharmaceutical industry and the CFDI investigators. Until the federal and provincial governments acknowledge and address the many concerns patients and physicians have risen about the deficiencies of the CDR and the unique characteristics of EDRD then it is unlikely that initiatives like the CFDI will be improved upon and implemented. Currently, it appears that the CFDI is a unique project that will not be replicated in the future. However the benefits of the CFDI can continue to be sustained, in a way that is well summarized by a participant:

> "I think the ongoing monitoring and collecting of data and information is very important and I believe the CFDI can continue to play a very important role with that, and I also believe that the CFDI can continue as a network or an expert body to develop and oversee the implication of treatment for Fabry disease in Canada. So while I would say the program as it is... I can't see why it would be replicated or transferred but I do see a way of modifying the CFDI so it provides value going forward (DR3)."

The federal and provincial governments also need to look at what is being done internationally with respect to EDRD. Those policies should not be blindly followed but investigated as to what they have been designed to do and what they are actually doing, and then be evaluated as to whether they could be implemented in Canada. To date, such research has not been performed. It is unreasonable to believe that Canada can fund EDRD research as the United States does, but it is not unrealistic to think that the provinces cannot collaborate together to provide national access to these drugs, so that no person in Canada will go untreated and suffer because of the cost of drugs. After all, as one participant commented, "if [27] member states in the EU came together, certainly 10 provinces and three territories could come together (PR1)."

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APPENDIX A: QUESTIONS FOR STAKEHOLDERS

Questions for Mark Embrett's research study: "Evaluation of Canadian Fabry Disease Initiative."

Thank you for participating and contributing to the research. Mark Embrett will present to you the following questions during your interview. Please answer with complete honesty. Remember all your answers will be anonymous and held in confidence.

If you do not wish to answer particular questions please contact Mark Embrett by phone or email.

Participant questions for Mark Embrett's research study: "Evaluation of Canadian Fabry Disease Initiative."

Thank you for participating and contributing to the research. Mark Embrett will present to you the following questions during your interview. Remember all your answers will be held in confidence by Mark Embrett. Names and affiliations will not be attributed to any responses, unless you have agreed on the consent form.

If you do not wish to answer particular questions please let Mark Embrett know during the interview process, or if you feel more comfortable by phone or email.

The interview will be semi-structured, meaning that while the questions may not be asked in this particular order, all of these questions will be asked at some point during the interview.

1) A) Is the CFDI meeting its outcome goals? Explain.
   B) In addition to the stated project objective, what do you feel was the main purpose for the CFDI?

2) A) Are you on course to meet your stated goals and objectives?
   B) What would it take to meet the stated goals and objectives (e.g., how many patients, what types, over what period of time)

3) A) What are the strengths and weaknesses of the project from your perspective?
   B) What are the alternatives to CFDI that could provide the desired benefits and avoid some of the weaknesses?

4) A) Is the program equally effective for all participants? Is it not effective for any one group?
   B) How could the program be changed to make it more effective for [all] participants?

5) A) Can the program be replicated and transferred to somewhere else?
   B) Should the program be used with other conditions and other treatments?

6) A) Was it worth the investment?
   B) If the investment for continuance were not available, how else could the desired benefits of the CFDI be achieved?

7) Are there lessons from international orphan drug policies that may be adopted by the CDFI?

8) Were the appropriate participants selected for the study?

9) How would you describe the role of the Independent Scientific Oversight Committee?
   a) Is it an efficient body?
   b) Are their changes you would recommend? If so explain.
   c) Has the Scientific Oversight Committee been serving the intended role during the study?

10) Are patients treated fairly? Do patients feel they are benefitting from the project? If not, what would need to be done to provide desired benefit to participants?

APPENDIX B: EMERGENT QUESTIONS

1) What is the primary objective of the CFDI?

2) What information has the patients been provided about the CFDI?

3) In your opinion, what is the CFDI?

4) What is your opinion on ERT?

5) Are the guidelines inclusive enough for patients?

6) Are there characteristics absent in the CFDI that you would like to see included?

7) What was the driving force behind the CFDI?

8) Could the CFDI be used as a learning experience?

9) If Canada was going to try to develop a national policy an interprovincial collaboration would you see a role for methods of reimbursement, guidelines and monitoring?

10) How has the absent of having a lead sponsor affected the CFDI?

APPENDIX C: TABLE 1: WITHIN-CASE ANALYSIS PATIENTS

Theme	Categories	Codes	Quotations
Patient concerns	Ethical concerns, Alternatives to CFDI, Communication issues between physician and patients, Patient consultation, Key challenges to CFDI from patient perspective,	Patient issues, treatment, guideline issues, accessibility, Canadian situation, Resource Allocation, Information provided to patient. Patient issues, patient knowledge, Bureaucratic solution to reimbursement problem. What is the CFDI	- I've received nothing directly from the doctor, other than the forms I had to fill out at the beginning which was just information gathering. - As patients we don't know enough about it, I think that we, we are kind of in the dark, some of that may be our own fault, but we are kind of in the dark, the level of consultation with us is very low. -you have to go to these meetings with doctors when they call you; there is a lot of testing that's involved. They tell you this testing you will have to do anyhow, well that's not necessarily true. If there is a problem I will go to my doctor. But if there's not a problem I don't go. - I don't think in general the patients really understand what is going on. To them they just think they are getting ERT thank you very much. I've been trying to get it now I got it everything will be fine. - I think that's one of the key challenges, we are a tiny patient population and it will take the many years to determine that. - My concern with it is, shared by others on the CFA board, is it gonna accomplish what it's set out to accomplish, or can it with the small population base. And then the being a study is it, are patients getting the best treatment - In terms of all the other objectives, it is clear that the CFDI is not properly powered to learn any of this information, especially since the information from the Canadian database is not integrated with the international databases. - It is unlikely that this registry, in isolation of larger registries, can identify additional side effects and certainly to compare the effectiveness of the two drugs. - We believe in a nutshell, the data that will be generated or already ahs been generated by the CFDI over the course of time, won't be any different from what we already know, from the world wide registry. So to a certain extent, we think this is totally redundant.

Theme	Categories	Codes	Quotations
			- originally the federal provincial governments and pharmaceutical companies agreed to finance a temporary study in order to get information required by law to say this medication is efficient for this type of illness. But when we get that result that yes it is efficient which it already has been tested everywhere else in the world , so I don't know why it has to be tested again, - We have a board member who is male, in his mid twenties, early to mid twenties. He's not on treatment. We know what's gonna happen to his kidneys when he's not on treatment. So let's get him on it. His kidney's aren't bad enough yet. That doesn't seem good, that's just not right. - We (the CFDI) are asking this individual to sacrifice his health in order to collect data. I have a tough time with that. - Patients who wish to change products cannot. At the last meeting, a family was sobbing because they felt the drug (being used) was ineffective but they had no option for dosage escalation or change. Patients who should be on therapy and would be if they were in other countries are being denied access under the guidelines of the CFDI. The natural history arm is a poor excuse for keeping patients out of treatment. - Personally I didn't want to be treated differently, and we were definitely treated differently. - In the CFDI I was, I call it blackmail. I saw it as blackmail. Either you do it to you don't get the drug. SO I didn't have a choice. That does not happen with any other medication if I am sick I get a medication.
Negative characteristics of the CFDI	CFDI protocol,	Patient issues: weakness, design inflexibility, Weakness Strengths	- Inflexibility I would consider a weakness. and another one is that the criteria to get in is quite strict, and we should go closer to international criteria, as I've been told is less strict. - The fact that patients must be randomized to one of the two drugs is a major weakness, as well as the fact that they cannot change treatments, if the one they are on is not working. This is not only unethical, but it is also dangerous to patients. - The fact that the study does not allow for a continuation of the dosage study that Shire was

Theme	Categories	Codes	Quotations
			required to do as a part of the NOCC is a major weakness - The treatment guidelines have not been changed since 2005 Garrod recommendations, even though the 2007 Year 2 report and the Year 2 report have recommended changes. The problem is that the protocol cannot be changed without the agreement of sponsors, and there is no evidence that the researchers have advocated for a change to treatment guidelines. - the ones there were not too happy about the fact that because it's a study they couldn't change from one medication to the other, and they vary the dose, depending on the symptoms and there was not that much flexibility in it - I think that I absolutely, and this is personal, a waste of money to try and find all the answers ... just by looking within the walls of Canada, I think it is an absolute waste of money. - If it's a way patients can get on their drug I would say yes. Is it the and all, I think I've said before no - I am convinced that all the stakeholders don't think the CFDI is the right model. I am one stakeholder and I don't think, I have an opinion - One strength is that the registry is in all of the sites where drug is available. On-going monitoring and tracking of patient measures and outcomes are good goals.
Positive characteristics of CFDI	Strengths of CFDI, potential as ODP model	Model for an Orphan Drug Policy, strength	- one good positive thing is that its nationwide access as opposed to, the provinces actually work together on something - I think that monitoring in particular for drugs for rare disorders is an absolutely necessity. Because first of all the clinical data leading into a drug approval is already minimal. By definition rare means rare, so I think not only there needs to be ongoing monitoring
Patient objectives	Patient experiences before and during CFDI.	Patient objectives. Patient lobbying, accessibility, guidelines	one is obviously we would like to get funding through the publicly funded health care system for ERT for Fabry disease - As far as the CFA is concerned we have three key issues. One is the funding of ERT in the

Theme	Categories	Codes	Quotations
			publicly funded health care system, The next most important is what guidelines the patients have to meet to qualify for access ERT Our number three priority is ongoing monitoring , which is to a certain extent where the CFDI comes in. - But the bottom line is that patients want to know that effectiveness of ERT because they don't wanna take drugs or therapies that don't work. I've seen it time and time again, and it's disturbing. I have done well for my family, I got my daughter and brother on ERT, and I have a niece and nephew coming up sometime and they will be on the enzyme. So it has taken a lot of time out of my life but I had to do what I had to do. - when you've been living with symptoms for all your life and you already have to deal with that to cope with the pain that it causes you and in addition to that trying to fight on the political aspect of it. We can't ask all of these people, it's just sad - We see a national ODP address numbers of issues. One because of the situation with the high percentage of Fabry patients in NS, NS government Can't be penalized because it has 40 or 50 % of Fabry patients. Why should they be saddled with that burden or that cost. The federal government has to show initiative by address this issue from a reimbursement perspective. We also believe that the federal government has to kick start issues around making changes to help Canada's policy of reviewing and approving a drug for rare disorder and we went through this whole issue ourselves with the common drug review. - We believe the federal government has to take the lead in addressing a national policy and standardizing this issue across Canada so you don't have drugs available in certain provinces particularly for rare diseases. We also believe the federal government has to take the lead in an ODP to provide an incentive and a stimulus for companies to do research in Canada. - Set up a patient registry, as we have with Gaucher's Disease or the MPS I and II diseases

APPENDIX D:TABLE 2: WITHIN-CASE ANALYSIS CFDI INVESTIGATORS

Themes	Categories	Codes	Quotations
Primary Objectives	Access, treat patients	Driving force, primary objective, identification of patients, accessibility , study protocol	- the main objective was to provide...ensure that patients who had the most benefits with enzyme...with Fabry disease that had the most benefit from enzyme replacement therapy in Canada got access to the treatment - The purpose was to develop a long term outcome measurements and to develop a research protocol to achieve that so all of us drafted this and designed a research study and then implemented this in our individual regions of Canada. - The purpose of the CFDI is to find as many if not all of the patients that have Fabry disease. Meaning patients that have a proven pathological mutation, and to develop a going monitoring program and for those who meet treatment criteria, the reimbursement criteria, for treatment with enzyme would receive that enzyme through a central agency which is the university health network. - one of the objectives of the CFDI from viewpoint in Canada is that results of this study are going to inform government as to whether they should reimburse these drugs or - Number 1 Objective is to provide ERT to patients in Canada who we think would benefit from treatment. - the driving force behind the CFDI in the first place to get drug to patients To get Patients, Fabry patients...the one main objective is to get Fabry patients that have known Fabry disease on Enzyme replacement therapy, if they qualify to be on ERT. The CFDI was set up in a way to get drug to patient. This is not, this is not actually the expressed goals when you look at the objectives of the protocol

Themes	Categories	Codes	Quotations
Positive Characteristics of design	National coverage, access to treatment, physician communication	Strength, patient satisfaction, national coverage. Patient identification, heavy workload. ISOC, independence from industry , CFDI research objectives, patient equity	- We have no reporting bias, in our patient enrolment, you know, we have basically enrolled all Canadian patients, whether or not they are on enzyme. - I think that long term registry registration for these patients is another long term objective, they have. So you know really getting all the patients in one place in one data base in one area across Canada - . So you know really getting all the patients in one place in one data base in one area across Canada. - First of all, patients are extremely thankful that they got, it These are people that would have had it infused in a broom closet if that's how they needed to get it done. It's obviously life saving for them. - patient coordination in terms of a standardized treatment across the country, so the treatments are standardized so you don't have one doctor doing something and another doing something else - Communication is better because it all falls under the umbrella so it's better based as opposed to being individual, so if we didn't have this we would have some communication deficiencies - it is a well organized, structured approach that by the employment of rigorous enrolment procedure is going to not only ensure access to treatment but will shed important new information on the value of ERT in general and a comparison between Replagal and Fabrazyme in particular. - I think it's an amazing, I've been working with provincial governments for almost 20 years, and the way they are working on this is really unprecedented. Quite remarkable. - a big part of the study to is increasing the number of patients have increased - The turnaround time is very quickly and it is possible for a patient to be completely reviewed and be on ERT within several weeks of initiating treatment, an application

Themes	Categories	Codes	Quotations
			being made for treatment. - it provides for a centralized purchasing of drug product which increases the number of patients to a point that the government collectively through the CFDI and UHN can negotiate pricing so there may be economies to be made by bargaining on a larger scale. - I think the consistency of access to therapy is uniform across the country for all patients so patient's mobility is not affected. - (ISOC) I think they are playing an important role in oversight of the CFDI study and their comments have been helpful I think to us. I think it's a good thing. - - its allowing a very expensive study to be done that industry wouldn't do on their own right now since they are already licensed, and which ultimately may allow for reimbursement of these two products in Canada and achieve access to patients. - Almost 99% of our patients if you ask them how they feel on treatment they will answer I feel worlds better , I notice a huge difference but then we do still see patients who are on chronic pain meds, or who are progressing to renal failure, some of our patients are having strokes. - I guess the good part about the CFDI is that the patients seem to have a lot of buy in, I don't know if that's because I came in when they didn't have a lot of alternatives. But it was quite well embraced, patients are compliant. - For the patients it s very good because they get excellent follow up - identifying and bringing out of the woodwork, so to speak, all the other people with Fabry disease - Paving the way for rare diseases all over, internationally and provincial wide in that rare diseases can be treated within a budget. - I think definitely the unity of the project that brought the entire country together for

Themes	Categories	Codes	Quotations
			rare diseases and that every province follows the same set of guidelines. - their approach has been extremely respectful so I have tremendous respect for the ISOC - you are looking at standardizing care, - I think it sets up a great network for doing other studies in Canada through the CFDI network. - (ISOC) they have been extremely supportive of the study and that. I think they've been a good set of eyes to look at data and to look at the overall study itself to point out some things,
Negative Characteristic of design	Meeting CFDI outcome goals, Ethical issues, Limitation of a research protocol for access , the absence of a single sponsor	Weakness, patient issues, design inflexibility, physician issues, administration problems , CFDI in stasis , CFDI general effectiveness, funding issues , sponsorship	- I think one of the weakness is that it's a CIHR grant, - CIHR itself has been a major stumbling block. They've been very limiting for us and very restrictive. - We would make modifications if there was new evidence suggesting different patient groups should be treated, whatever. And we have done this every year, and they have yet to adopt any of the revised guidelines. So although we have 2008 guidelines, we are still working with the ones that were in place in 2006 which were actually written in 2005 - That's very frustrating; it's also a colossal amount of work. As far as weaknesses, the actual amount of work it is taking to get this stuff together, and not just from the coordinators, but I have to say personally, for physicians. It is a colossal amount of work, it probably doubles the amount of time I spend seeing a Fabry patient, by the time I get all their data entered onto the report forms, and all the additional assessments. - Somebody has to step up to the plate and say we are the sponsor for this project. We are tired, the doctors, I'm speaking on

Themes	Categories	Codes	Quotations
			behalf of the doctors now, but it very frustrating not to be able to identify one person who is willing to represent all of the players, and is willing to take responsibility and make decisions about sponsor. - in order to look at effects of treatment on those complications the only way to really look at those is to have a naturally history group, and although we have a large untreated cohort, you know it's the largest cohort, the untreated group, if they suffer a complication they get moved to the treated group - funding is an issue. And at this time I have no idea. - When they get randomize they get one or the other they don't get much choice for one or the other. And if one is not working they don't get a choice for one or the other. So they are feeling a little coerced. - first of all there is no single sponsor, perhaps one of the problems we encountered administratively was identifying the sponsor and we finally determined that there it was probably the provincial drug programs so from the standpoint from clinical drug research the process is different from each provinces. - any modifications to protocol any reports, any thing that has to be done, needs to be cleared by all the stake holders before it can be considered cleared. And that is cumbersome. - I think it is a response I think it is a cumbersome response because the purpose for getting it organized and the mechanism by which it occurs was very slow. - I think one of the issues that makes it difficult is that it is done under a research protocol which means there has to be a great number for ethic review committees render their judgment for their own area. - Not only that but there was never a process defined as to how the funding would be renewed and what would be the process to make that decision. It's still not been

Themes	Categories	Codes	Quotations
			defined, as far as I'm concerned
Model of ODP	lessons, transferability	Model for ODP (orphan drug policy) Recommendations to improve the CFDI, strengths	- It's nice to now long term outcomes, so from an educated research point of view. It's great to know that. We should know that for all our drugs, we don't have a venue for that, So I think my short answer is yes, It allows the drugs to get paid for, It allows a funding model that everyone has a stake in. The federal provincial and the drug companies know for you know have a vested interest in it. And it then gives some long term data, you've got long term safety data, you've got outcomes, you know everyone is looking for outcome studies these days, so yes. It's something that would be beneficial - I think in some ways you need a sole physician that is dedicated just for it I think the data entry may not be as great because, I've gone out to the site every six months to ensure data entry is in, we also have a report we have to do once a year, and an annual meeting once a year, so there's twp dialogues once a year, and the push is on for people to put their data in and that stuff - Yes you could replicate it, uhm, but it would need to be different. You couldn't just say you have to go on this treatment, have patient options, the options change, and a little more flexibility within the protocol. - Would be an advantage of center in Canada and care of patients. I don't disagree with the data collection; it does have to be funded. But the mechanism by which we've set them up need to change. Become more user friendly. - There's a learning curve, I hope this experience, if it s going to be repeated with it his model of government and industry sharing funding in a study. I think we have learned to put some structure in place before hand to support this. - as far as a model in the future, it seems, a model that incorporates, reimbursement to the companies, monitoring of drug effectiveness and guidelines for inclusion

Themes	Categories	Codes	Quotations
			rather than just open door to any who has the disease. Those seem to be important components. - Paving the way for rare diseases all over, internationally and provincial wide in that rare diseases can be treated within a budget. Yes, I definitely, think it's possible. I think it's a bit...because of the database that needs to be run with the CFDI, I can understand them needing their own private data base, but I can definitely see that not being perhaps needed for other diseases. It is very much administration heavy with running the database, although it does seem to be cost efficient. But that tend to be mostly administration type work. So I think with other diseases, with them being rare, if they meet the guidelines, and if they're reviewed by a board or a panel on a yearly basis I think that would be adequate.
Origin of CFDI	Bureaucratic solution to reimbursement problem, drug reimbursement,	Driving force, weakness, Canadian situation (nonCFDI), strengths	- they needed some kind of unique venue to, it's almost an excuse, you know, the study part was an excuse to get the drug covered, - so essentially, they tries to solve a reimbursement problem by designing a research study and funding the problem through that method, instead of just deciding to reimburse the drug. - This is the government's way to ensure they are getting value for their money. - it was clear that Canada did not have the mechanism for dealing with reimbursement of very costly drugs for rare diseases and there was a lot of pressure and the time the CFDI was initiated there were patients in Canada who had been taken off treatment because there was not a funding mechanism in place, these patients were patients that had been on treatment during clinical trials. - But then when Fabry disease came along it was quite clear that the governments were quite leery about paying this large amount of money and patients were going off treatment being the companies gave up and said we ware not going to give you any more medication the provinces said our evaluation says you don't meet our criteria

Themes	Categories	Codes	Quotations
			for funding and patients started going downhill. Some patients in Canada actually died - There was demand from patients to get access to therapy because there was not other therapy for Fabry disease. Here you had these therapies patients were on it and drugs were licensed in Canada but patients couldn't access unless they were one of the very few who had coverage under their private drug insurance - that's right and they all got cut off, because companies in a move designed to put pressure on government, withdrew all access to so called compassionate use drug, so in other words. They were providing drug free to certain patients, and that all stopped on at the end of April 2005, I believe it was, and interestingly it happened on the same day. What a coincidence. - There was not any funding available and our patients were all cut off. So for us the bottom line was to get patients on treatment. - you know the CFDI started of as an idea as a money laundering scheme and a way to get around the common drug review

APPENDIX E: TABLE 3: WITHIN-CASE ANALYSIS PROVINCIAL GOVERNMENTS

Themes	Categories	Codes	Quotations
Lessons	Alternatives, Model as ODP. Characteristics of the CFDI	Learning experience, model for ODP, driving force of CFDI,	- We get learning s we actually get to study it. We get real life experience. We also get negative things. - There was no other product available but within a framework that would allow decision makers to also assess the product is being used and to inform future decisions. - In the absence of that how do we potentially, particularly when a new drug comes to market there are short terms studies or the studies themselves have surrogate markers. All these questions come up and we get challenge as to how do we make a funding decision associated with that particular product and we talk to our advisory committee, they are looking for a detailed study. From a program policy standard we ask how feasible it is to conduct a study within a public drug program, so this has been a great learning around. It is something we can do, cost a little bit. Some of the long terms, what are the time requirements to administer these programs. So it gives us a bit of perspective around what are the mechanics in place to successfully move these studies forward. So it's a good learning experience for everybody. - I see it as a starting point not a solution - Yea, as these models are being developed we are actively sharing information between the jurisdictions because there is no point in Alberta creating model that contradicts what Ontario is doing. We would get hammered over the discrepancies.
Government challenges	Situation for provinces in Canada for EDRD, **Challenges for EDRD**	Government issues, recommendations that could improve CFDI, government alternatives, protocol, weaknesses Canadian	- from a program perspective I am a bit cautious that we are bringing in so many restrictions that it becomes difficult to manage the funding of the product and it become difficult to get product to the patients - We have the challenge of equality. We agree that may be the only product, but does it work?

Themes	Categories	Codes	Quotations
		situation (non CFDI), driving force of CFDI,	- Where the evidence that is available today? Or the clinical practice associated with using this particular drug, may be out of scope with the published evidence as part of the review of the product. So it's a challenge we have regardless - It is in a much broader context and I think that that's the part the initiative is actually a representation of the challenges associated with drug programs across the country on a number of fronts. - You overlay that with the fact that no one individual can afford to spend 250000 on an ongoing basis. That's not sustainable. You overlay that with different provincial; ministries having different public benefit designs. So you add those three variable and you have a very unique situation that for required some resolution. - once you've given something it is extremely difficult to take it back, that's the point I was trying to suggest. You cannot link research with reimbursement decisions. The research deals with the case or advances the case but it often doesn't refute the fact that access is gonna have to continue to be provided. Let me repeat that the research can advance the reimbursement decision right? But it often cannot reverse the access that's already been granted. - I think the barrier becomes first of all if there's value in the profit and there profit in the front end then the question becomes how do you negotiate, what price are you prepared to pay. - It is in a much broader context and I think that that's the part the initiative is actually a representation of the challenges associated with drug programs across the country on a number of fronts. - It's because it's an expectation. You set the expectations at the front end, so give me give me give me, okay you have it. Oh it kills me, you should have known better. If you didn't know better you're still alive now so what changed. A little more information gotta be positive, it's not bad right? Moral persuasion. - One of the key pieces that we need to take a

Themes	Categories	Codes	Quotations
			look at are, how do you initiate therapy; you also want to assure you are not causing harm by enrolling patients into these trials. So I think the criteria are important. It is also just as important to know when to stop these medications. - If we are to do these kind of one off arrangements, we can't lose sight of what is happening on the broader national sector. - When you talk about shared funding it becomes a challenge. Who holds the money, where do you get it, who pays who. But it's not insurmountable. It just make s it , the jurisdictions are always, strained with resources, so, simpler is always better for us. - It's the consistency of first of all, making the clinical decision based on the evidence. Then secondly we have to have a consistent approach of reimbursement. - With the long term goal of potentially developing some pooled risk sharing strategy across jurisdictions. That was the intent behind and that is the much broader policy discussion to have in this country about whether or not we should have one pharmaceutical plan across all regions. So that's the stage for you.
Positive characteristics of the CFDI	Program benefits, physician specialists	Strengths, national coverage,	- We worked with the other jurisdictions and other jurisdiction that may not have a detailed review process like Ontario, could certainly rely on our ability to share information and put these proposal forward together as a group. That was one of the strengths across jurisdictional work. - The strength is that it is a core group of researchers that are able to enrol patients into the study with a fairly self contained group of individuals. And I think the fact that the evidence is being collected and the numbers they are getting seem to be relatively strong. I think we will start seeing good information coming out of their research group. - I think it was something all the provinces could work toward to provide a funding recommendation for the product. - I think these are one of the few proposals that we have in place that does have a

Themes	Categories	Codes	Quotations
			research protocol as the underpinning part of the agreement. That is something that when our reviewer are looking at a product always wish these are the studies they should have done this in the first place

APPENDIX F: TABLE 4: WITHIN CASE ANALYSIS PHARMACEUTICAL PROVIDERS

Themes	Categories	Codes	Quotes
CFDI challenges	Outcome Goals, statistical issues, ethics	Pharmaceutical issues, Statistical problems, weakness, protocol, database and monitoring, CFDI in stasis, sponsorship	- It's unclear how the CFDI will be able to assess the degree of impact of ERT, when there is no corresponding control group. - I would say the other things, and that's something the investigators know themselves is the lack of statistical power is an issue, obviously due to small sample size. Which make the study under powered at least for many years going forward to really detect any difference between the treatment groups, in cohort 1B. - I do think that one of the issues with this is the fact that patients are somewhat forced to consent to enter into the trial. In order to get access to therapy. - One of the fundamental questions is whether or not the Canadian database is going to add any additional to what is being monitored, looked at internationally. With a much greater number of patients. - Again I touched on weaknesses but really I am concerned that there's an unlikelihood to be able to properly assess the effect of ERT, because of no control group - Regionalism, or the regional approach to health care in Canada, is a problem, it's a big problem, for not only enzyme replacement therapy but for oncology drugs, uhm, if you have a condition in one province you may get access where in another province you don't get access - I mean the protocol was written in 2006 and it's now 2009, a lot more has been learned globally about the symptoms and treatment of Fabry disease, and none of those global learning have been incorporated into the treatment criteria. - It's a very unique situation. It's caused by the fact that there's no, there're operating in a vacuum, there's no policy to guide governments, its a rare disease so there's not a lot of clinical information so people claim its never good enough so we have to

Themes	Categories	Codes	Quotes
			do more research. - Now maybe people will hope time will go on forever and eventually if you have a long enough randomization you may come up with an answer, but an underpowered study is a self fulfilling prophecy to repeat the claim there is no difference. Number 2 is that there's no sponsor. There's issues with government in this study. Data from 3 years says ago there is no difference; data from last month there is a difference. No sponsor becomes a problem. The world has changed its like building an airplane while you fly it. It's a difficult situation because the Canadian health care system is ins shambles I studied it for years. It doesn't work; nobody wants to hold the ball.
Lessons	Learning experiences	Model for ODP, pharmaceutical issues	- I guess one of the alternatives would be to take a step back and look at what some of the most outstanding research questions, clinical research questions are. What exactly are the outstanding research questions and to have the protocol modified in some aspect to realty try to answer those questions. - absolutely any initiative of this magnitude should be used as a learning experience, and a lot of good things have happened as a result of the CFDI being put in place, but certainly and I do think there could be a role for the CFDI going forward as well. I would agree that it could be used as a learning experience. - So what you are asking is whether or not having access to therapy and having the CFDI are they 2 separate things, I believe they should be separated. - as I mentioned before I think the ongoing monitoring and collecting of data and information is very important and I believe the CFDI can continue to play a very important role with that, and I also believe that the CFDI can continue as a network or an expert body to develop and over see the implication of treatment for Fabry disease in Canada. So while I would say the program as it is I can't see why it would be replicated or transfer but I do see a way of

Themes	Categories	Codes	Quotes
			modifying the CFDI so it provides value going forward.
Model for a program to access EDRD	Transferability, replication for a national program for EDRD	Model for ODP, strengths, monitoring, guidelines, and reimbursing	- I would think whether there was a provincial - program or national program I believe the treatment guidelines would be an important component and certainly the ongoing monitoring of patients I also agree is extremely important and the answer would be yes. - I think this a fundamental part of the research, to me, I will be open and honest, the CFDI is being implemented at significant cost, there is a need for additional process and resources, and the way that it is currently set up I believe there is significant unlikelihood that new information on the treatment or disease will be found. Given this I don't see why it would be ideal to move this to other treatments or to other jurisdictions outside of Canada. - I don't think it's a good idea no. This is a bureaucratic solution to a reimbursement problem, the issue is that the provinces were not gonna fund Fabry patients to receive enzyme replacement therapy. - is this a good model for other rare diseases? And I would say no it's not a good model. Principally because it is fixing a problem but there's a better way to fix this problem and that problem is just to have a national rare disease policy and right up front make some commitments about achieving global standards in the treatment of people with rare disease and follow that policy,. Don't make up clinical trials that are really meant to solve a reimbursement issue. If you need to do research, do research, if you need to reimburse reimburse. But don't use research to solve the reimbursement question. Can you take a flawed process and apply it to other rare disease? I hope not. It's assuming that there are no problems and this is a good model for other are disease, I think it's a terrible model - Absolutely I think the issue is not confusing reimbursement with research, that's the fundamental flaw. My feeling is

Themes	Categories	Codes	Quotes
			separate reimbursement from research, If there's a research question lets address it. Let physicians freely choose what medication they want to treat there patients with and do it that way.
Positive characteristic of the CFDI	Strengths	Strengths, national approach	- By far and I can't emphasize this enough patients are getting access to therapy, thought he CFDI they are getting a good level of high quality care. Prior to the CFDI there was no funding mechanism, patients were not getting access, and this is definitely the strength of the CFDI project. The other thing that we touched on too, the data is being captured and recorder, I can't comment on the quality of the data. But it is being captured and recorded which is another strength. But in terms of the CFDI, while the strength is a national approach, which is good. - I agree with collecting data good, using data to support treatment good, putting a shining light on treatment data good,
Negative characteristics of the CFDI	Criticisms, problems,	Weaknesses, statistical problems, CFDI general effectiveness	- Again I touched on weaknesses but really I am concerned that there's an unlikelihood to be able to properly assess the effect of ERT, because of no control group - I mentioned before the patients being forced to consent to the trial to receive treatment - I don't think we've touched on this and there's been an inability of physicians outside of the CFDI to prescribe ERT even if they meet guidelines. - Also both physicians and patients lack any choice to determine which ERT to use or receive and part of the reason that's important is since the CFDI was started there's been a significant amount of clinical data that has come out, and that may provide physicians with a guide on which ERT would be of best interest to their patients, right now any patients entering into the trial would not have that choice. So to us we see that as a weakness. - The weakness is in that the, there is an inability to treat all Fabry patients or there's an inability to treat Fabry patients, who are

Themes	Categories	Codes	Quotes
			suffering from the disease with symptoms, that would be treated in other countries, but because of the extremely strict criteria that are dated. - This is a bureaucratic solution to a reimbursement problem, - I think that is a fundamental downfall because its, very awkward to offer reimbursement to force patients to do a trial when researchers don't have clinical equipoise. -The question that the investigators think they are going to resolve can never happen because it's underpowered. There's no way there statistical methods can answer those questions - But there is nobody who wants to do it, because it's the wrong design, the wrong setup to get someone to be a sponsor for his study. CIHR ideally would have been the best; they don't want to do it. The problem is if you have a study that is not measuring, doesn't not have the precision to note the difference between the treatments, in other words,

APPENDIX G:TABLE 5: BETWEEN CASE ANALYSIS

Theme	Categories	Codes	Quotes
Importance of CFDI	National scope, positive characteristics, Canadian policies	National program, database and monitoring, accessibility, guidelines, communication network, identifying new patients, patient equality, strengths,	- One strength is that the registry is in all of the sites where drug is available. On-going monitoring and tracking of patient measures and outcomes are good goals. - patient coordination in terms of a standardized treatment across the country, so the treatments are standardized so you don't have one doctor doing something and another doing something else - By far and I can't emphasize this enough patients are getting access to therapy, thought he CFDI they are getting a good level of high quality care. Prior to the CFDI there was no funding mechanism, patients were not getting access, this is definitely the strength of the CFDI project. The other thing that we touched on too, the data is being captured and recorder, I can't comment on the quality of the data. But it is being captured and recorded which is another strength. - I think defiantly the unity of the project that brought the entire country together for rare diseases and that every province follows the same set of guidelines. - The first one for me is that we got a whole bunch of people who weren't being treated back on treatment. And I couldn't care less what you do with the information, get us back on treatment. Step 1. - well it is a well organized, structured approach that by the employment of rigorous enrolment procedure is going to not only ensure access to treatment but will shed important new information on the value of ERT in general and a comparison between Replagal and Fabrazyme in particular. - Its fairly comprehensive, we are providing it to all the patients that need it; we are selecting clinical data in a very rigorous fashion. We have an electronic data base which will help us learn a lot about Fabry disease and response to ERRT, we are comparing the two drugs head to head. We are looking at safety aspects of this, we are doing some sub studies looking at antibody formation against the enzyme,

Theme	Categories	Codes	Quotes
			- it provides for a centralized purchasing of drug product which increases the number of patients to a point that the government collectively through the CFDI and UHN can negotiate pricing so there may be economies to be made by bargaining on a larger scale. - When a new drug comes to market there are short terms studies or the studies themselves have surrogate markers. All these questions come up and we get challenge as to how do we make a funding decision associated with that particular product and we talk to our advisory committee, they are looking for a detailed study.
CFDI in stasis	Protocol problems, restrictive guidelines, ethics,	Administrative problems, CFDI in stasis, heavy workload, weaknesses,	- you've got so many parties involved there, you've got certainly well over ten different people who need to focus their attention on the issue and say yes to it. That's awfully cumbersome and reduced the likelihood of success - The treatment guidelines have not been changed since 2005 Garrod recommendations, even though the 2007 Year 2 report and the Year 2 report have recommended changes. The problem is that the protocol cannot be changed without the agreement of sponsors, and there is no evidence that the researchers have advocated for a change to treatment guidelines. - Most other countries have international guidelines that are based on the latest data. - So any modifications to protocol any reports, any thing that has to be done, needs to be cleared by all the stake holders before it can be considered cleared. And that is cumbersome. - The whole thing is a bit cumbersome. Our last year or two annual report had a request for an amendment to the protocol, minor stuff. As well it had new guidelines for ERT from this expert committee... So this goes to ISOC and then after that the protocol has to go to the sponsors to see if they agree. That included industry as well as government, I don't know how long that process is gonna take. Could take years, some as the ERT revises guideline as who we are going into treat and not treat has to be approved by the sponsor before we as physician can implement it within the study. These things will have to go to the local ethics board as well. After I get approval from the financial sponsor so this could take a year maybe two by the time you get

Theme	Categories	Codes	Quotes
			approval from the provincial government... It has to go to the ethics board right across the country for all our sub sites and regional sites, there' s 9 sub sites and 5 regional sites, that's fourteen. It could be a couple of years before we get paperwork approved. The study could be over. It's very cumbersome process. - The weakness is in that the, there is an inability to treat all Fabry patients or there's an inability to treat Fabry patients, who are suffering from the disease with symptoms, that would be treated in other countries, but because of the extremely strict criteria that are dated. I mean the protocol was written in 2006 and it's now 2009, a lot more has been learned globally about the symptoms and treatment of Fabry disease, and none of those global learnings have been incorporated into the treatment criteria.
Reimbursement problem solved with research	Inflexibility protocol, outcome goals	Inflexibility, CDR ineffectiveness, accessibility, guidelines, CFDI outcomes 1-6 Primary objective, driving force of CFDI, pharm issues, patient issues, physician issues, government issues, patient coercion, patient equality, statistical problems, bureaucratic solution to reimbursement problem	- so essentially, they tries to solve a reimbursement problem by designing a research study and funding the problem through that method, instead of just deciding to reimburse the drug - My concern with it is, shared by others on the CFA board, is it gonna accomplish what it's set out to accomplish, or can it with the small population base. And then the being a study is it, are patients getting the best treatment. -In terms of all the other objectives, it is clear that the CFDI is not properly powered to learn any of this information, especially since the information from the Canadian database is not integrated with the international databases. - In terms of all the other objectives, it is clear that the CFDI is not properly powered to learn any of this information, especially since the information from the Canadian database is not integrated with the international databases. - Randomization of patients to one drug or the other is totally unacceptable because there are differences in response on individual basis and there is no hope that enough patients could be enrolled to provide a comparison through a randomized assignment. - I think that from the CFA perspective and we've said this all along that there are too few patients to study in Canada, so why don't you

Theme	Categories	Codes	Quotes
			use and participate in the internationally community either the Fabry registry or the Fabry observation survey, which has much more data and many many more patients. - I think it's totally inappropriate that Canadian Fabry patients who want access to ERT through the publicly funded health care system are force to become a member or register for the CFDI. I think that's totally inappropriate. - If you qualified you were automatically randomized. We totally disagree with that, we think it's illegal and unethical. The patient should have some, he s a member of the decision making process. - When they get randomize they get one or the other they don't get much choice for one or the other. And if one is not working they don't get a choice for one or the other. So they are feeling a little coerced. Now, if they are not doing so well on it, cause normally what you would do in the real world, the physician would say, okay let's try a bigger does. Or if something is not working let's stop it and try you on something else. - A research study is a research study; accessing product is a reimbursement issue. They are different issues. - The other thing that really bugs me about the CFDI is that it's a publicly funded study. That's what I think it is. You're way out of bounds here, way out of bounds. K. Publicly funded health care should not be doing research on drugs. That's the pharmaceutical industry's problem. - This is a bureaucratic solution to a reimbursement problem, the issue is that the provinces were not gonna fund Fabry patients to receive enzyme replacement therapy
Alternatives	International models, alternative methods,	Gov alternatives, international database registries,	- I think as a nation we really need to start looking, base on what the EU is doing, what the US is doing, and other developed countries and participate in gathering of information, and added to international registries and not starting from scratch. - 50 member states in the EU came together. Certainly ten provinces and three territories could come together

Theme	Categories	Codes	Quotes
			- With the exception of the comparison of the two products, all of these objectives can be addressed with a registry that is connected to international registries, where the data could be pooled for meaningful effects. - The approach used by the UK in their Rare Disease Commissioning approach (where patients are put on individual treatment contracts and continuance is based on achieving desired benchmarks); the Netherlands which provides for individual protocols, including early entry to treatment, dosage manipulation, and additional follow up. Most other countries have international guidelines that are based on the latest data - the federal government has to kick start issues around making changes to help Canada's policy of reviewing and approving a drug for rare disorder - the federal government has to take the lead in addressing a national policy and standardizing this issue across Canada so you don't have drugs available in certain provinces particularly for rare diseases. - The federal government has to take the lead in an ODP to provide an incentive and a stimulus for companies to do research in Canada. - Now I'm not saying it's wrong to do research but if you are going to do research you need to address the questions that we know are relevant today. - Yes, I definitely, think it's possible. I think it's a bit...because of the database that needs to be run with the CFDI, I can understand them needing their own private data base, but I can definitely see that not being perhaps needed for other diseases. - One way of looking at this, and there are many examples from other countries that provide access to therapy along with high quality healthcare, - Can you take a flawed process and apply it to other rare disease I hope not. It's assuming that there are no problems and this is a good model for other are disease, I think it's a terrible model. I think the best model is being developed in the European union.

APPENDIX H: TABLE 6: CHARACTERISTICS OF THE CFDI TO BE APPLIED, DROPPED, OR ADDED

Applicable CFDI components	Removable CFDI components	Non CFDI components
- national access - national guidelines - ongoing monitoring - national data collection - standardized care - communication network of physicians - outside of CDR jurisdiction	- Research outcomes - inflexible protocol - randomization of treatment - access to drug dependant on enrollment	- long term funding arrangements - a single leading body in charge of administration - patient involvement at a decision making level