The Clinical Adoption of anti-CD19 CAR T-cell Therapy in Alberta: A Historical Review and Retrospective Comparative Case Study

by

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Abstract

This thesis details the adoption of anti-CD19 CAR T-cell therapy in Alberta from 2018-2021, during which time a commercial (tisagenlecleucel) and investigative (ACT-C01) CAR T product were implemented as standard of care and under a clinical trial, respectively. Information was gathered through stakeholder interviews, primary source documents obtained from Alberta Health Services employees involved in the adoption process, and peer-reviewed and grey literature acquired by targeted database searches. Herein, we provide a timeline of the events and processes at both centres; a comprehensive list of the stakeholders and their relationships; and an analysis of the challenges of and enablers to adoption using the Consolidated Framework for Implementation Research. Potential approaches to assessing the outcomes of the adoption process across each site from a health system perspective are proposed, and lastly, limitations of the study are acknowledged and future research avenues proposed.

Preface

The research project of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name “Challenges of and Enablers to Implementation of Adoptive Lymphocyte Therapy”, No. Pro00064788, on June 14, 2016. This thesis is an original work by Zackariah Breckenridge. No part of this thesis has been previously published.

Acknowledgements

I would like to thank the following organizations that supported this research including the Women and Children’s Health Research Institute, University of Alberta, CellCan, BioCanRx, Stem Cell Network, and Alberta Cancer Foundation. Furthermore, I am grateful to the participants of this study who generously gave their time and insights, as well as the countless others involved in the translation and implementation of CAR T without whom none of this would be possible. Lastly, I humbly commend those whose lives have been touched by this disease and confess how deeply honored I am to have had the opportunity to contribute to the war effort against these most insidious of maladies.

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Glossary

ABMT: Alberta Bone Marrow Transplant Group (Calgary)

ACF: Alberta Cancer Foundation

ACH: Alberta Children's Hospital

ACHF: Alberta Children's Hospital Foundation

ACIT: Alberta Cellular & Immunotherapy

ACT-C01: Alberta Cellular Therapy - Cancer 01/Made-in-Alberta CAR T

ACTM: Alberta Cell Therapy Manufacturing (U of A)

ADM: Assistant Deputy Minister

AH: Alberta Health

AHS: Alberta Health Services

APL: Alberta Precision Labs

B-ALL: B-cell acute lymphoblastic leukemia

BAS: Business Advisory Services (AHS)

BiTE: Bi-specific T-cell engager

BMT: Bone Marrow Transplant

BSO: Biosafety Officer

CADTH: Canadian Agency for Drugs and Technologies in Health

CAPCA: Canadian Association of Provincial Cancer Agencies

CAR T: Chimeric antigen receptor T cell therapy

CBS: Canadian Blood Services

CCA: Cancer Care Alberta

CCI: Cross Cancer Institute

CCO: Cancer Care Ontario

CD19: Cluster of differentiation 19

CDR: Common Drug Review

CEO: Chief executive officer

CFIR: Consolidated Framework for Implementation Research

CHU: Sainte-Justine University Hospital Centre

CIU: Clinical investigation unit

CLL: Chronic lymphocytic leukemia

CNE: Clinical Nurse Educator

CTL: Cell Therapy Laboratory

CTL: Cytotoxic T-lymphocyte

CTL019: Kymriah/Tisagenlecleucel

CTOCC: Cell therapy operations coordination committee

CTP: Cell therapy product

CTPOC: Cell therapy provincial oversight committee

CTRCC: Cell therapy research coordination committee

CTRSA: Clinical Trial Research Services Agreement

CTU: Clinical Trials Unit

ECCC: Environment & Climate Change Canada

ELT: Executive Leadership Team

EXC: Excellerate Canada

FACT: Foundation for the Accreditation of Cell Therapy

FDA: Food & Drug Administration

FMC/TBCC: Foothills Medical Centre/Tom Baker Cancer Centre

FTE: Full-time equivalent

HC: Health Canada

HMR: Maisonneuve-Rosemont Hospital

HREBA: Health Research Ethics Board of Alberta

H(S)CT: Hematopoietic (stem) cell transplant

iBSO: Interim biosafety officer

IIT: Investigator-initiated clinical trial

LDC: lymphodepleting chemotherapy

LYHE: Lymphoma and Hematology Group

MAPP: Maximum Average Potential Price

MIA: Made-in-Alberta

MM: Multiple myeloma

NABMT: Northern Alberta Blood and Marrow Transplant Program (Edmonton)

NACTRC: Northern Alberta Clinical Trials Research Centre

NHL: Non-Hodgkin's lymphoma

NOC: Notice-of-compliance

NOL: No-objection-letter

NSN: New Substance Notification

PCODR: pan Canadian Oncology Drug Review

PCPA: pan-Canadian Pharmaceutical Alliance

PHAC: Public Health Agency of Canada

PI: Principal Investigator

PM: Project Manager

PMH: Princess Margaret Hospital

PMPRB: Patented Medicines Price Review Board

QMCR: Quality Management in Clinical Research

R/R: Relapsed or refractory

RG2: Risk Group II

SOC: Standard of care

SOP: Standard operating procedure

T0: Basic science research (preclinical)

T1: Early clinical research (phase I, I/II clinical trials)

T2: Late phase clinical research (phase II and III comparative, pivotal trials)

T3: Research into regulatory marketing approval, reimbursement, implementation and integration

T4: Population-level health outcomes and impact research

TMD: Temperature Monitoring Device

UAH: University of Alberta Hospital

VO: Victoria-Ottawa

Chapter 1: Introduction

This thesis consists of two original papers: first, we develop a timeline of events by document analysis using historical research methods and determine the relationships of stakeholders involved in the clinical adoption process. Next, we partition the timeline into phases based on salient events using Rogers Innovation Diffusion Process[1] and validate and supplement the timeline using interview data.

Building on the results of the initial paper, we identify the major challenges and enablers to the implementation of CAR T in Alberta according to the views of interview participants in paper two. We then fit each challenge and enabler to a construct within the consolidated framework for implementation research (CFIR), and their influence on the implementation of each product is described. We then discuss methods for assessment of implementation success in relation to the CFIR and provide lessons learned and recommendations for the adoption of similar innovations.

Chapter 2: Historical Review of the Clinical Adoption of CAR T in Alberta

Background

Anti-CD19 Chimeric antigen receptor T cell therapy (CAR T) is a cellular immunotherapeutic modality currently approved for sale in Canada for the treatment of patients with B-cell neoplasia. After decades of research starting with the first publication in 1989[2], initial clinical results in 2010[3], and marketing approval in 2017[4], CAR T cell therapy is now standard of care[5] in lymphoid malignancies of the B-cell lineage[6]. The novel complexity of the modality necessitates coordination between site and manufacturer, education and consideration of a host of issues shared by expensive biologics and patient-specific medicines. Factors including product cost, patient-specific batch manufacturing, clinical stakeholder diversity and severe side-effects make implementation of the technology an exemplar for study by healthcare policy researchers worldwide[7–9]. Novel bio therapeutics with similar product characteristics face the same translation and implementation challenges as CAR T. With growth in momentum to reshape the pharmaceutical-academic-clinical interface to reduce costs while improving access to therapies that lead to better patient outcomes, it is timely to chart the history of the adoption of CAR T in a real-world setting.

This study offers a real-world account of the co- implementation of two CAR T products (Alberta Cellular Therapy - Cancer 01 (ACT-C01)/Made-in-Alberta (MIA) CAR T and tisagenlecleucel/Kymriah) introduced into a large single-payer, publicly funded healthcare system during a time of unprecedented change and uncertainty. In so doing, we provide a unique insight into the challenges faced when bringing novel therapies to patients at a formative point in time for healthcare systems and present the lessons learned during this process by industry, clinicians, clinical researchers and healthcare administration. This timeline may also be useful to technology developers attempting to estimate time required for various milestones, and to funders in forecasting return on investment into early-phase clinical research.

The objectives of this paper are to:

1. Develop a timeline of salient processes and events by analysis of administrative documents;
2. Identify and describe the key stakeholder groups and individuals involved in the adoption process and their relationships to one another;
3. Supplement and validate the timeline using interview data;
4. Partition the timeline into phases within the Innovation-Diffusion Process based on key events and processes.

Methods

This study was approved by the University of Alberta Research Ethics Office. A historical research approach[10,11] was used to trace the history of the adoption of CAR T cell therapy in Alberta. This entails a rigorous archival critical analysis (including internal and external criticism) of numerous documents (contracts, meeting agendas and minutes, training and marketing materials, reports, decision requests, etc.), analysis of key informant interviews, and development of the narrative. Data sources were considered primary if they were published by employees of the organization itself or were personal communications (i.e. emails). Documentation (minutes, reports, business cases) related to the development of the academic CAR T product and implementation of CAR T at AHS sites were provided to the author by key informants. A portion of study participants also consented to provide relevant emails to the researcher. Key events in commercial CAR T federally, and in other provinces were identified through secondary data sources (non-AHS documentation or emails) acquired in grey literature searches using Google™. The majority of this data comes from reports by provincial bodies and news releases. A total of 72 documents were included in the final analysis (below).

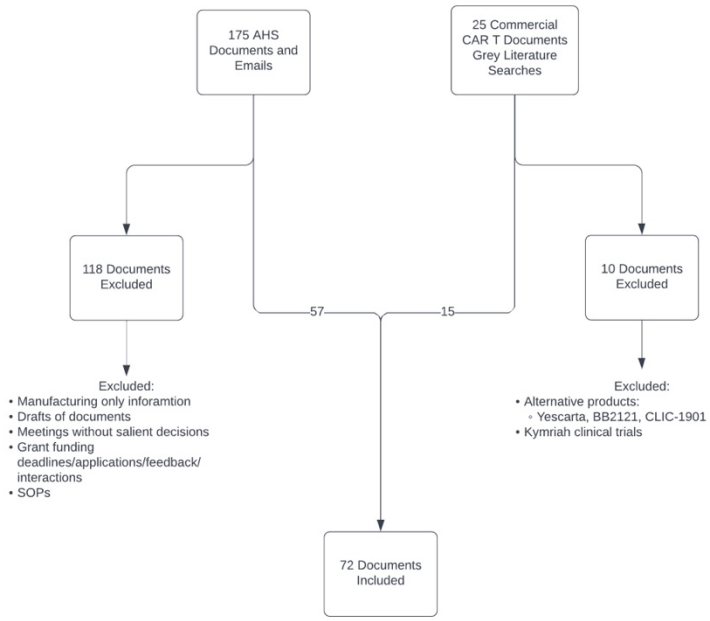

Figure 1. Overview of Timeline Data Collection Strategy

Documents were catalogued in an Excel workbook and key decisions, dates, events and outcomes were recorded in the summary. Data were extracted from source with a data extraction template form (Appendix 1.1) that captured chronological and content information in Microsoft Excel. Events were annotated as unique to the commercial product (Kymriah) or academic product (ACT-C01) or common to both. To be included in the analysis, documents must have discussed CAR T adoption in Alberta, or Kymriah in Ontario or Quebec between February 2018 and December 2021. The relevant chronological data from documents were copied and pasted into Microsoft Office Timeline to construct a timeline automatically. During the document analysis, key decision makers, influencers and stakeholders were flagged for the subsequent interview phase of this research and assigned to one of six stakeholder domains (CTP Developer, Institution, Clinical, Health System Administration, Regulator, and Funder). Groups that interacted in timeline events were captured using open-source Lucid chart online software to form a stakeholder network (Figure 6).

Semi-structured interviews were conducted to supplement the timeline and validate the sequence and dates of important events (as well as to collect data for a related project). Purposive sampling was used based on stakeholders identified in document analysis and prior relationships between

the researchers and the clinical, industry and academic community. During interviews, participants were asked to describe their role in CAR T adoption and to elaborate on the chronology of important events or processes in which they were involved or of which they were aware. The dates and sequence of particularly salient events or those without significant data from document analysis were investigated further through interview prompts. The master interview guide is available in Appendix 1.2. Any themes arising from the interviews that affected the chronology of events were captured using NVivo software using the coding scheme in Appendix 1.3. Participant responses were compared to processes and events described in literature, and discrepancies were noted.

Incorporating a second data source in this way identified several important events not found through document analysis, and in particular illuminated activity by executive and management-level decision-makers. Better understanding stakeholder motives and decisions made at this level enabled the researcher to more accurately partition the processes and events using the framework, which utilizes information of this nature to describe the diffusion of an innovation through an organization.

The timeline was partitioned according to the framework of the Five Stages of the Innovation Process organization (Agenda-setting, Matching, Redefining/Restructuring, Clarifying, Routinizing)[1] and presented below. Key points in the partition were: a) the point at which the decision to adopt the technology is made where implementation begins (#3), and b) the date of delivery (#4) where the processes of clarifying and routinizing begin as the innovation is used for the first time. The use of this framework was particularly suitable to our needs as it includes a re-invention phase, which allowed us to capture the development of the implementation of locally manufactured CAR T in greater detail.

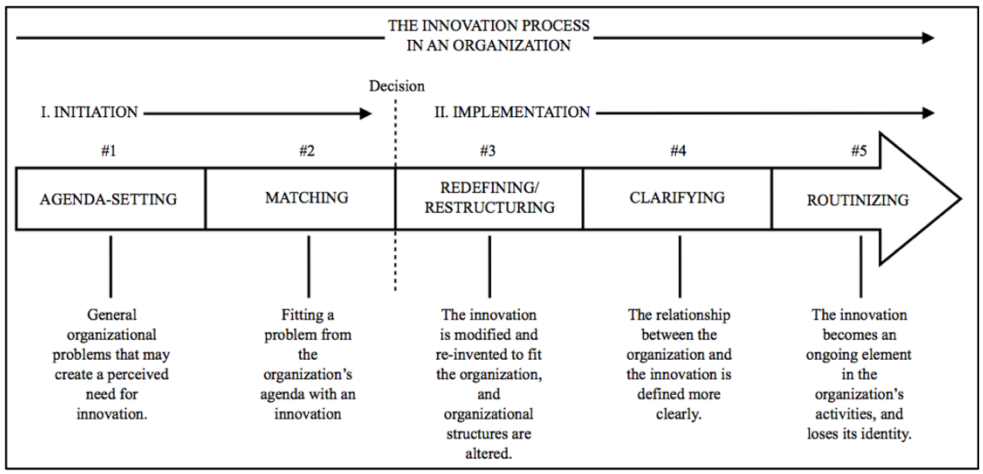

Figure 2. Innovation Diffusion in an Organization (From Rogers, 4th Edition)

Results

Initiation: Agenda-Setting & Matching Stages

February 2018 – February 2019

Summary

The adoption process begins with the initiation phase, where the stakeholders decide on the priority (agenda-setting) of the introduction of the innovation in relation to other issues and engage in the process of selecting the appropriate action (matching). In this case, initiation is seen as activity in three domains: industry (Novartis), the clinical community (Lymphoma and Hematology Group (LYHE)), and healthcare administration (Cancer Care Alberta (CCA)). The first milestone is Novartis' new drug submission for Kymriah to Health Canada in February 2018. During the summer following, Novartis engaged the Government of Alberta (GOA) in negotiations which accelerated after they received their corresponding Notice-of-compliance (NOC) for Kymriah in the fall of that year. In parallel, the clinical community in Alberta identified CAR T as a priority at their annual meeting in March and participated in a series of meetings over the summer to persuade leadership of its benefit and to discuss an implementation strategy. CCA administration conducted a rudimentary needs assessment and approved the decision to adopt CAR T in June 2018. Concurrently, CCA and the clinical community made decisions to provide interim access through an investigator initiated clinical trial (IIT), and suggested the development of a business case for Alberta Health (AH) to fund the supportive care aspects of the new clinical trial and commercial product across the province. The Principal Investigator (PI) developed early clinical trial materials and hired staff over the winter of 2018-2019 while seeking additional resources and securing

institutional commitment. The next section begins with the initial meeting of the CCA CAR T working group in which a more complete needs and risk assessment is presented to the clinical community and leadership for review.

Unmet Need

Anti-CD19 CAR T therapy was introduced at the Cross Cancer Institute and Foothills Medical Centre to serve patients with relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL) and Non-Hodgkin's lymphoma (NHL). These two diseases arise from neoplasms within cells of the B-cell lineage that share common molecules called surface antigens. Where along the lineage the mutation in the cell of origin occurs determines the disease that develops[12]:

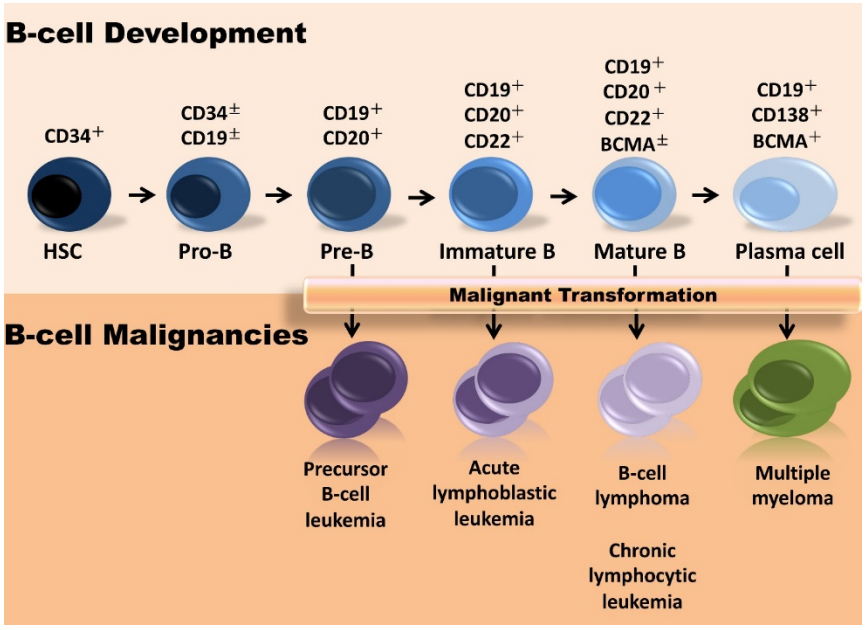

Figure 3. Development of neoplasia along the B-cell Lineage

Coincidentally, the clinical translation of CAR T therapy loosely recapitulates this process, with initial results in B-ALL, followed by B-cell lymphoma, and most recently multiple myeloma (MM). Based on the estimates of the current population and the 2021 projected age-standardized rates of incidence, it was anticipated that 1000 new patients a year would be diagnosed with NHL in the catchment area of these two centers which include the Northwest Territories, Saskatchewan and non-lower mainland British Columbia. Of these 1000 patients, roughly half would be cured and half would fail first line therapy[13–15]. Collectively, those failing first line would have a median

overall survival of 6.3 months[15]. Figure 4 is a simplified estimate of patient numbers and indications where CAR T is approved for use in NHL. Of note, commercial manufacturers have recently demonstrated survival benefits in second line as opposed to salvage chemotherapy and transplant for those with relapsed or refractory (r/r) disease after first line therapy[16].

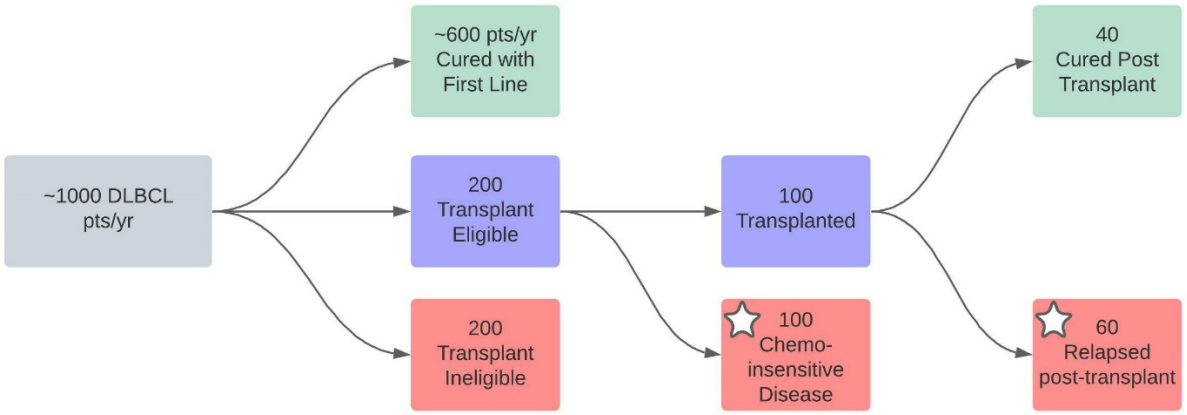

Figure 4. Non-hodgkin's lymphoma (NHL) treatment pathway and estimated patient numbers. Stars denote where CD19 CAR T is currently indicated.

Patients in two other populations discussed in this thesis also received (or were eligible for) CAR T therapy in Alberta: adult and pediatric relapsed B-cell acute lymphoblastic leukemia patients. Together, these cohorts comprise a significantly smaller number than relapsed/refractory NHL, with adult B-ALL patients representing the majority. After first relapse, and prior to referral for CAR T, the expected median overall survival after relapse is 8.4 months, with a 24% chance of survival[17].

Clinical Awareness

Novartis released the results of their primary analysis of their pivotal study (JULIET) of Kymriah in NHL in December of 2017, bringing international attention[18]. The product had already become the first ever commercially available CAR T cell product when the US Food & Drug Administration (FDA) approved it for use in pediatric B-ALL in August of the same year. The Alberta clinical community being aware of these results, raised the CAR T issue for discussion at

their next scheduled the Alberta Hematology Tumor Group (LYHE) meeting in April 2018[1]. The minutes show CAR T was flagged in the breakout sessions for lymphoid malignancies as having clinical utility in multiple myeloma (MM), NHL, and B-ALL. In particular, myeloma physicians agreed a statement was needed in the new guidelines on immunotherapy and CAR T, while Hematopoietic Cell Transplant (HCT) physicians who would likely see CAR T first, voiced concern about the anticipated cost of $2.5 million/patient. As part of the proposition of new guidelines section of the meeting, the Hematology Section Chief of the Edmonton Zone (the first champion of the adoption process) described CAR T as an "emerging therapy for NHL, B-ALL, myeloma and other malignancies" and asserted it "will soon be a standard of care".

Importantly, at this meeting there was acknowledgement of multiple paths to adoption of CAR T in Alberta through: 1) an investigator initiated clinical trial of a locally manufactured CAR T product (ACT-C01) initially launching in Edmonton led by a second clinical champion and 2) a pharma-sponsored trial with possible introduction as standard of care afterward in Calgary. Officially, CAR T was reported as one of five strategic priorities for 2018-2019, and a follow-up meeting was planned to specifically discuss CAR T implementation.

Two non-CAR T issues were also raised as potentially impeding implementation of CAR T cells: the province-wide rollout of an electronic health record over the next several years[19] and the increasing size of the hematology portion of the provincial cancer drug budget, which was approaching fifty-percent of the total budget in 2017, an increase primarily being driven by drug costs.

[1]The (Ly)mphoma and (He)matology (LYHE) / Alberta Hematology Tumor Group annual provincial meetings provide a venue for clinicians to review new evidence and recommendations, agree on revisions to provincial treatment guidelines, and compare results between centers. They are primarily attended by medical oncologists and hematologists but also included high level managers in Cancer Care Alberta, directors of individual hospital departments (including pharmacy and laboratory), and industry representatives.

Administrative Decision

Two months later, the pivotal meeting attended by seven leading provincial hemato-oncologists, as well as executive members of Cancer Care Alberta, was held mid-way between Edmonton and Calgary. Also present were representatives of the Calgary cell therapy research community, Alberta Cancer Foundation (ACF) and Alberta Children's Hospital Foundation (ACHF). The objectives of the one-day meeting were to: summarize the field at present; develop a strategy for introducing CAR-T and other cell therapies in Alberta; summarize existing infrastructure and further needs (facilities, equipment personnel); decide what diseases, targets, constructs should be pursued; assess clinical trial options (IIT, industry, hybrid); and establish a formal working group.

The group confirmed the promising clinical utility noted previously and agreed on a priority of indications: "CAR-T cell therapy should be standard of care for childhood B-ALL patients who have relapsed, and is a reasonable option for adults with chronic lymphocytic leukemia (CLL) who have relapsed; it is also a promising treatment for lymphoma and myeloma at the time of relapse." Importantly, they also came to a consensus on the grading of expected adverse events and agreed that cellular therapy should be standard of care and funded operationally rather than as a research study.

Initiation Decisions

The afternoon turned toward funding when the group had a presentation from a senior executive of Cancer Care Alberta titled the 'Alberta Health Perspective'. Summarily, AH considered CAR-T therapy experimental, and would not be approving applications for out-of-province or out-of-country treatment at that time. Fortunately, out-of-province treatment was available through clinical trials. Funding, for the therapy itself, was available through Novartis, although patient travel was not. The group thought it would be important to clarify what AH would cover for out-of-province pediatric treatments as these were available through clinical trials in Ontario and Quebec.

With growing clinical momentum behind adoption and recognition of funding and access challenges prior to market approval, the group proposed more "discussion about how to get the message out more widely to other leadership in AH and AHS about how to align with other

provinces' decisions to fund/not fund out-of-country treatment". Attendees also speculated on how AH would respond when the therapy was no longer labeled "experimental" (Red Deer Meeting Minutes, 2018), since Novartis was expected to receive regulatory approval in the autumn of 2018. The recommendation of the group was "for clinicians to write letters to [CCA executive] with a copy to the CEO of AHS, in order to communicate with appropriate government members regarding requests for funding".

Having formally made the decision to adopt, the group began to match their institutional needs and priorities to the innovation, starting with a debate as to whether or not to wait for local clinical trial experience or simply initiate development of a clinical program in anticipation of commercially available CAR T products. They ultimately determined "the province was positioned well to develop a local [clinical] program, and it would be beneficial to proceed with a clinical trials program initially" (Red Deer Meeting Minutes, 2018), acknowledging however, that beginning the process without positions from Health Canada nor the pan Canadian Oncology Drug Review (pCODR) on the approval or the cost-effectiveness of a commercial product was risky.

As a first step, the CCA executive recommended developing a business case to attain grant style funding from AH for "a one-time proof of concept trial, and long term provincial program"--highlighting the hesitancy of upper management to fully commit to funding a new program. The executives suggested the business case be developed internally, with financial support for its creation from the ACF and the ACHF as "[they] have funded the development of business cases that span across AHS programs and facilities, and are interested in exploring this opportunity further". The first working group meeting was recommended for early autumn, coinciding with the marketing authorization of the first commercial CAR T product, Novartis' Kymriah (tisagenlecleucel).

Local manufacturing was raised again as an alternative to commercial CAR T, as both cities had laboratories that could hypothetically produce CAR T products. The approach was pioneered by a collaboration between American academic centres and European cell therapy manufacturing vendors, and had demonstrated feasibility at multiple sites using a point-of-care delivery model[20] in pediatric B-ALL and NHL[21,22]. Some of the purported benefits included a 75% reduction in

price, half the time from apheresis to re-infusion and access to a fresh instead of a cryopreserved product. It was decided that a working group would be established "to support the automated generation of CAR T cells at a local level" and a project manager was suggested to help build the clinical program and support clinical trials, which could be funded through a partnership with the ACF.

As part of the matching process the clinical community reviewed the expected barriers to adopting CAR T: 1) Edmonton's Northern Alberta Bone & Marrow Transplant (NABMT) program was not accredited by the Foundation for the Accreditation of Cellular Therapy (FACT) for an HCT program, whereas Calgary's Alberta Bone Marrow Transplant (ABMT) program was, although neither were FACT accredited for Immune Effector Cell delivery (under which CAR T would eventually fall); 2) NABMT relies on Canadian Blood Services (CBS) to process and store their blood products[2] whereas Foothills Medical Centre (FMC) had an attached Cell Therapy Laboratory with whom they had worked closely for years and; 3) both sites had a lack of prior experience with CAR T or IEC therapeutics through clinical trials, despite ABMT being FACT accredited (although the site had experience with BiTE therapy, and one physician had direct clinical experience with CAR T stateside). Notwithstanding the optimism around CAR T outlined out in the meeting minutes, one interviewee (P14) recalled some controversy over the perceived therapeutic effectiveness at the meeting:

> *"…the Calgary group was a little bit pessimistic about the capability of CAR-T cell therapy and I came away from that a little bit frustrated and decided that if that was the case, I was just going to start doing CAR T cells myself in Edmonton… That's when the light bulb went on-- thinking here we had all the necessary resources and infrastructure to actually do this in Edmonton without having to rely on a pharmaceutical. And that's what really the incentive to go ahead was." (P14)*

A Calgary perspective from another provider gives their view:

[2] As of April 2018, NABMT now has the internal ability to collect cells by apheresis, a procedure historically performed by Canadian Blood Services staff within the CCI.

"…my impression was that the primary impetus for the clinical trial was to kind of get a foot in the door for Edmonton… FACT accreditation is tied to cell therapy labs pretty intricately as well and having a history of an allogeneic HCT program in Calgary and a good relationship with Alberta Precision Labs (APL), I think that's one of the key kind of driving forces to this."(P8)

At this point, the adoption of CAR T in Alberta began to bifurcate into an IIT route in Edmonton and a commercial path in Calgary at the implementation stage due to prior conditions and the intervention of clinical champions. Going forward, both groups would share the application for clinical funding for a business case and some operating procedures; however, the IIT would face additional challenges unique to the clinical translation of cell therapy (Figure 3).

Two months later in August, a second meeting was held to further discuss the IIT ACIT001/EXC002. Updates included a new draft clinical trial protocol, successful AHS Research and ACF reviews, contract negotiations between the Northern Alberta Clinical Trials and Research Centre (NACTRC) and vector manufacturer Lentigen, and the announcement of the ACF sponsored clinical trial project manager who would formally be hired in January of 2019, but had been consulting since spring of 2018. The Cross Cancer Institute (CCI) also hired a project manager under Bone Marrow Transplant (BMT) to assist with FACT accreditation around this time as well.

After the meeting, news of a potential program quickly moved beyond the leadership to include hospital administration. Dissemination to higher level administration was, in one case, facilitated through a job talk given by one of the oncologists (a third clinical champion) who would later become a major clinical contributor to the business case. After the presentation, he was challenged by a hospital director who had not been involved in the earlier discussions at the Red Deer Meeting:

"So very shortly after the meeting in Red Deer, we started having quite advanced talks about getting all this going…the woman who used to be the executive director [of internal medicine]… so that's an operational position within the Foothills Hospital. So she's the unit manager's boss, basically … said, 'Whoa, whoa, whoa,

whoa, hold on, hold on. This sounds like it needs extra funding.' So we had all of the nuts and bolts in the clinical pieces all put together and then we were told, OK, you need a business case and that needs to go all the way through AHS and up to Alberta Health… I was talking to her once a month about this. And so I was a little bit surprised when she turned around and said, 'well, we can't do this unless you get extra funding'. And that was what sent me back to cancer care to say, OK, I've hit a roadblock." (P8)

In late October 2018, CCA executives were re-engaged by government to ascertain the state of readiness to deliver Kymriah in the pediatric population and their theoretical monthly capacity. This led to an informal discussion between leading pediatric oncologists as delivery at both sites would represent a departure from the traditional model that sees the vast majority of pediatric cell therapy patients are treated in Calgary. The discussion was further complicated by conflicting assessments of the impact of disparate FACT accreditation and associated clinical resources at each site.

Commercial Product Reviews

While the clinical community drove adoption through Cancer Care Alberta with philanthropic support from ACF, pharma drove it from above through government and payers from Ontario and Quebec eastward. The process began in Canada when Novartis filed a New Drug Submission to Health Canada for Kymriah in both adult NHL and pediatric B-ALL in February of 2018[23], when Alberta physicians formally decided to support the adoption of CAR T in Alberta at their annual meeting. Concurrently, the Canadian Association of Provincial Cancer Agencies (CAPCA) and the Canadian Agency for Drugs and Technologies in Health (CADTH) co-hosted a CAR T meeting in which they created the CAR T-cell Adult Consensus Guidelines. In April 2018, CADTH announced that "given the unique aspects of these health technologies, CADTH will review CAR T-cell therapies through its health technology assessment process for medical devices and clinical interventions, and not through its pan-Canadian Oncology Drug Review (pCODR) or Common Drug Review (CDR)"[24]. They continued to justify the process change by saying it was "implemented in direct response to feedback from federal, provincial, and territorial Ministries of Health and the Canadian Association of Provincial Cancer Agencies (CAPCA), and is consistent

with that being taken by several other health technology assessment bodies, including the Institut national d'excellence en santé et en services sociaux (INESSS) in Quebec."

Novartis received its Notice of Compliance and marketing authorization for both indications in Canada on September 5th, 2018[25] and immediately it began to engage provincial payers in pricing negotiations who were organized through "a provincial and territorial government committee that included CADTH and the provincial cancer associations to talk about CAR T and all the price negotiations that were going on with Novartis". A CCA director recalled:

> *"So they were all getting in touch with government directly and saying, You know, we've got these amazing products and you know, you guys need to be getting geared up to be able to deliver them. So that's when government came to cancer care and said, hold on. We're getting all this stuff, all this conversation about what's going on and we need more detail."(P10)*

Until that point, and again for later CAR T products, pricing negotiations with payers had been on a province-by-province basis through the pan-Canadian Pharmaceutical Alliance (pCPA) by individuals at the drug plan manager level.

However, with Kymriah, for reasons that remain unclear, the pCPA did not review the file and instead the government of Ontario led an interprovincial agreement on behalf of all provinces with the aim of producing "a negotiation mandate by the end of September" according to one interviewee (P10). This brought higher level government officials in Alberta to the negotiating table. According to an industry representative:

> *"My sense is that [government] wanted it to be at the drug plan leader level because it was the ADM level mostly that were negotiating it so, and normally a pCPA file would never be with ADMs. It would typically be at a drug plan manager level in oncology. So what they do is they have someone from the drug plan and then someone from Alberta Health. So they have sort of an oncology and a non-oncology person. And so that's kind of the model they have across all the provinces.*

So it was an odd one to be done. But what I do know is that it was at the ADM level." (P13)

In the pricing negotiations the Alberta government was represented by the Provincial Services Unit in Pharmaceutical and Supplementary benefits who had been actively gathering information on CAR T from clinicians and convened another distinct government/payer group called the Alberta Working Group in September. Although no documents exist around the nature of activities of this group, an interviewee was able to clarify their role:

"They were afraid of not having a coordinated approach to getting CAR T cell therapy into Alberta, either from a commercial standpoint or with the clinical trial. And I think what they were worried about was maybe a conversation happening here that was a sidebar that would kick off something that somebody over here didn't know about but needed to know about in order to get the right things in place to make it happen effectively." (P10)

By November 2018, pricing negotiations with provincial payers led by Cancer Care Ontario (CCO) and CADTH review were ongoing. Also, at this time, Novartis had cleared review by the federal Patented Medicines Review Board (PMPRB) who recommended to reimburse conditionally on the reviewed price of $482,550/dose[26]. Decisively, in January 2019, the Health Technology Expert Review Panel of CADTH recommended "the provision of tisagenlecleucel in Canada, with conditions, including a reduction in price" however, according to a Novartis spokesperson "the price for Kymriah was currently being finalized" in January[27]. According to CCA meeting minutes, Novartis was still in pricing negotiations with AH in February. The final price the Government of Alberta agreed to pay for Kymriah, and any arrangements or payment schemes made remain unclear; however, the PMPRB reported the first date of sale of Kymriah in Canada to be May 24, 2019 and a maximum average potential price (MAPP) of $539,035.1100/dose[28].

Implementation I: Re-invention

March 2019 – December 2019

Summary

The implementation phase of the timeline begins in March with the administrative decision to adopt the innovation. Evidence of this decision is the first meeting of the CCA body formed to implement the innovation in March 2019, the CCA CAR T Working Group. During this period, it is revealed that additional funding would be needed to launch a province-wide CAR T program by hospital administration in Calgary, and the clinical champions work with CCA administrators to determine extent of additional investment and the creation of a business case to be submitted to Alberta Health to meet this end. In Edmonton, due to several factors acting in concert, the innovation is substantially reinvented to meet institutional needs utilizing local resources leading to the development of the clinical trial ACIT001/EXC002. Lastly, during this phase for clinicians, access to CAR T became more pressing due to their difficulty referring patients for treatment out-of-province or –country.

Cancer Care Alberta

After the official decision to adopt CAR T was made in Red Deer in June 2018, ten months elapsed until the first official meeting of the CCA CAR T Working Group was convened by CCA Strategic Planning. Although the working group was established to deliver CAR T only, its mandate significantly expanded by the time it was first presented by the CCA Director of Strategic Planning. The (eventually approved) governance structure would enable them to oversee the entirety of cell therapy province-wide going forward. The initiative would be led by the newly created Cell Therapy Provincial Oversight Committee (CTPOC) and would report only to the highest level of the CCA, the Executive Leadership Team (ELT). The group was then sub-divided into 'operations' and 'research' coordination committees (CTOCC and CTRCC), and further subdivided by site into local coordination committees (ACH, UAH/CCI, FMC/TBCC).

The CTPOC aims were as follows: 1) foster collaboration across CCA, and with other key stakeholders in the development of an Alberta CAR-T cell program; 2) recognize key challenges to providing CAR-T across the province from a trial and practice perspective; 3) provide recommendation to CCA ELT and guidance to AH in moving the program forward/overcoming barriers to establishing a CAR T Program, 4) understand the emerging patient needs and help to

accelerate access, and 5) facilitate coordination of clinical and research activities across the province and across disciplines.

At the meeting, CCA leadership presented the results of a province-wide needs assessment and identified several sources of risk (Quality/Safety, Policy/External Environment, Human Capital, Infrastructure, and Finance) in adopting CAR T. CTPOC recognized the risk to quality and safety inherent in the increased impact on ICU capacity as 'medium to low' with mitigation through "provincial coordination of patient scheduling to ensure Inpatient and ICU capacity" (CAR-T Working Group meeting materials, March 2019). A second risk was one of policy, external environment and public confidence if Alberta were not chosen as a delivery site for CAR T and pointed out that "early understanding of the potential costs/benefits will situate Alberta to respond quickly to new opportunities that arise in this area" as a mitigation strategy. Third, they recognized a risk associated with the need for specialized inpatient training and proposed "establishing initial and ongoing training protocols for management of CAR T cell patients". In terms of infrastructure, they assigned a medium to low risk and noted the acquisition of a Miltenyi Prodigy (automated cell culture device) would help with redundancy in manufacturing for local CAR T production, again looking to "provincial coordination of patient services" to mitigate this risk. The last source of risk was under- or overestimating the cost of delivery that would be mitigated through "engaging all operational stakeholders who would be impacted by CAR T delivery at an early stage so a comprehensive budget plan can be developed". A subsequent meeting was organized for one month later in April 2019.

In the meeting material (the first iteration of the business case), CAR T was framed as "involving intensive clinical and ancillary resources" and cited CADTH's recently published recommendations that Kymriah be delivered in FACT accredited HCT centers, nodding to ABMT in particular. It was also assumed that there was "potential for critical care admission in 25-30% of patients lasting 5-10 days post CAR T- cell therapy, versus standard end-of-life care with salvage chemotherapy and supportive care measures" (CAR-T Working Group meeting materials, March 2019). A fundamental implementation strategy was proposed based on an estimated incidence of 30-60 patients per year, which would see ACH treat all pediatric patients and the ABMT program at TBCC/FMC treat the adult patients over the next two years, while the CCI

sought FACT accreditation with the expectation of the CCI taking a portion of adult patients in the future.

During the second CAR T Working Group Meeting, in April, the committee was updated on work in the IIT sphere and the governance structure was formalized. Membership of the CTOCC was approved and it was made responsible for **"**oversight and coordination of cellular therapy treatment across the province" and "for ensuring the ACH, UAH/CCI and FMC/TBCC had the necessary resources and support to provide high quality cell therapy" (CAR-T Working Group meeting minutes, April 2019). The CTRCC membership was approved and mandated to **"**identify and coordinate resources needed to carry out translational cell therapy research in their local area in alignment with the vision and strategic direction of cellular therapy research in the province" (CAR-T Working Group meeting minutes, April 2019).

This involved input from CCA leadership and oncologists in both centers during the spring of 2019, and the first draft of the business case was circulated to stakeholders in mid-May, including funding for new positions in Quality Assurance and Nursing Education at both centers, and clinical funding for new apheresis infrastructure at ABMT. The annual Hematology Tumor Group Meeting was held in May 2019, and had less of a focus on CAR T. It was only mentioned in Objectives for 2019-20 as "CAR-T therapy: open new trial and programs at both sites".

Business Case

In the summer of 2019, CCA Strategic Planning continued to develop the business case with support from AHS Business Advisory Services (BAS). The final request seen by the clinical representatives in November included additional positions in nursing, medicine and QA support, as well as additional apheresis infrastructure and novel operational costs associated with assessing CAR T patients, primarily lab, pharmacy and diagnostic imaging. The price of the drug was not included in the business case. The business case was submitted to the CCA ELT in November and reviewed with the CEO of AHS:

> *"[AHS Executive Leadership] was leading the meeting and I finished my little presentation and at the end of the meeting, she said, well, you know, it's a no brainer. We have to do this." (P8)*

After ten months, BAS and CCA completed the business case and submitted it to Alberta Health in late January 2020. The lead reflected on the experience:

> *"I think looking back on it, if this executive director who I was talking to had actually said at the outset, gosh, this sounds like it needs a business case. I, you know, I would have asked for help to make a business case. But you know, it was it was all completely new to me. And so I think ideally we should have started the business case sooner. I think we lost a good six months by delaying writing the business case." (P8)*

ACIT001/EXC002 Sponsorship

The initial steps to develop and launch the IIT which would deliver their Made-in-Alberta CAR T cell product had occurred during the winter of 2018-2019. By March 2019, around the time of the first CAR T Working Group meeting, the PI and project manager (PM) formed Alberta Cellular & Immunotherapy (ACIT) to manage the project and the PI had drafted a clinical protocol and finalized budget. At this point, ACIT took these materials to the CCI IIT launch team within the Clinical Trial Unit (CTU) to notify them and involve them in the study launch process. Surprisingly, at this meeting, the managers of the CTU told ACIT that because the trial may involve treating patients experiencing adverse events at the University of Alberta Hospital (critical care/hematology/neurology), they felt it inappropriate for the CCI to sponsor the study.

Moreover, the two regulatory managers of the CTU told the investigator and PM that the CTU wasn't interested in assisting with study-related activities of any sort including: the Health Canada submission of the clinical trial application (support for the clinical trial protocol, development of the manufacturing data), local ethics submissions, institutional operational approvals, or the

development of a clinical database (electronic data capture system). Furthermore, the CCI CTU would not provide the service of clinical trial nurses to collect the data, financial or budget analysts, coordinators to enter it, or content experts to review the safety of the study.

CTU management recommended the PI undertake these activities with assistance from Quality Management in Clinical Research (QMCR), a University of Alberta group that monitors clinical trials with no experience in oncology, drug manufacturing, launching clinical trials or existing relationship with the CCI. Fortunately, as a group QMCR had experience with electronic data capture systems (REDcap) where the CTU still employed a paper-only system. QMCR also had experience monitoring (but not launching) multicenter IITs whereas the CTU did not. While initially reticent, the QMCR manager committed to supporting the project manager and PI in launching the study and secured support from NACTRC to have the U of A officially sponsor the study.

Why the CCI CTU decided not to sponsor or assist with the clinical trial was an area of debate in the interviews. The PI felt that it was due to a lack of resources and experience:

> *"Part of the concern was whether or not the Cross has the personnel and HR to be able to handle some of that sponsorship responsibility and the fact that they'd never done so up to this point. So as a result, due in part to a lack of familiarity and lack of confidence similar to that of the inpatient delivery, we then had to turn to the U of A as the alternative. In hindsight, that actually probably worked out better anyway just because U of A as a sponsor was familiar with doing a multicenter trial." (P14)*

One of the senior level executives at CCA recalled the interaction with the CCI CTU as such:

> *"…it was it was kind of weird. So that basically then left a gap. So, you know, one of the interesting things is that CTU was very, very definite about what it did do and what it didn't do. But I still think there was some gray areas of, as you say, if they had confidence in the PI and whatever, and it was something that I think they*

understood how to do: get the patients, decide how to randomize them, get them randomized to a new drug or whatever it is, and then off we go. But I think CAR T, I mean, I remembered actually talking to [CTU Manager X], oh, ages ago, and she was like, "Oh my God, we don't know what this is, and we can't get any answers and so on and so forth" like, OK, but I said, you wouldn't be on your own here. Like there's village of people trying to make this work, and I think they just put their hands up and said "nope not for us". (P10)

With little help from the CCI and limited assistance from QMCR, ACIT began developing their own clinical research program to address the translational challenges to the project (Figure 5) with seed funding from the Alberta Cancer Foundation. At this time, ACIT was also developing the CTP manufacturing process with ACTM, so the number of stakeholders in the project began to quickly increase (Figure 6).

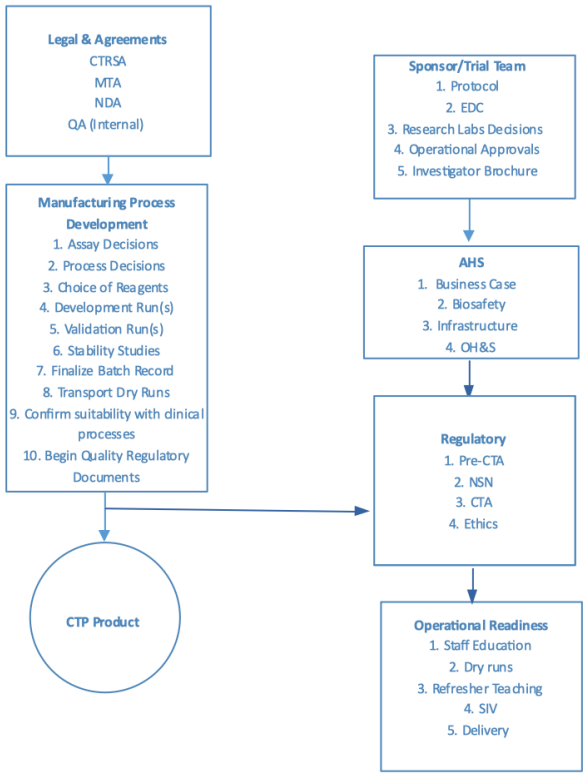

Figure 5. Translational Challenges: 'Alberta Cellular Therapy Investigator Initiated Trial (IIT) to Alberta Health Services (AHS) Translation' Pathway

Fortunately, after being refused funding for the clinical costs of the trial by the CTU and individual hospital departments, ACIT was able to voice the resource needs of the CCI's future CAR T program to AHS through business case being developed by CCA and AHS Business Advisory Services (BAS).

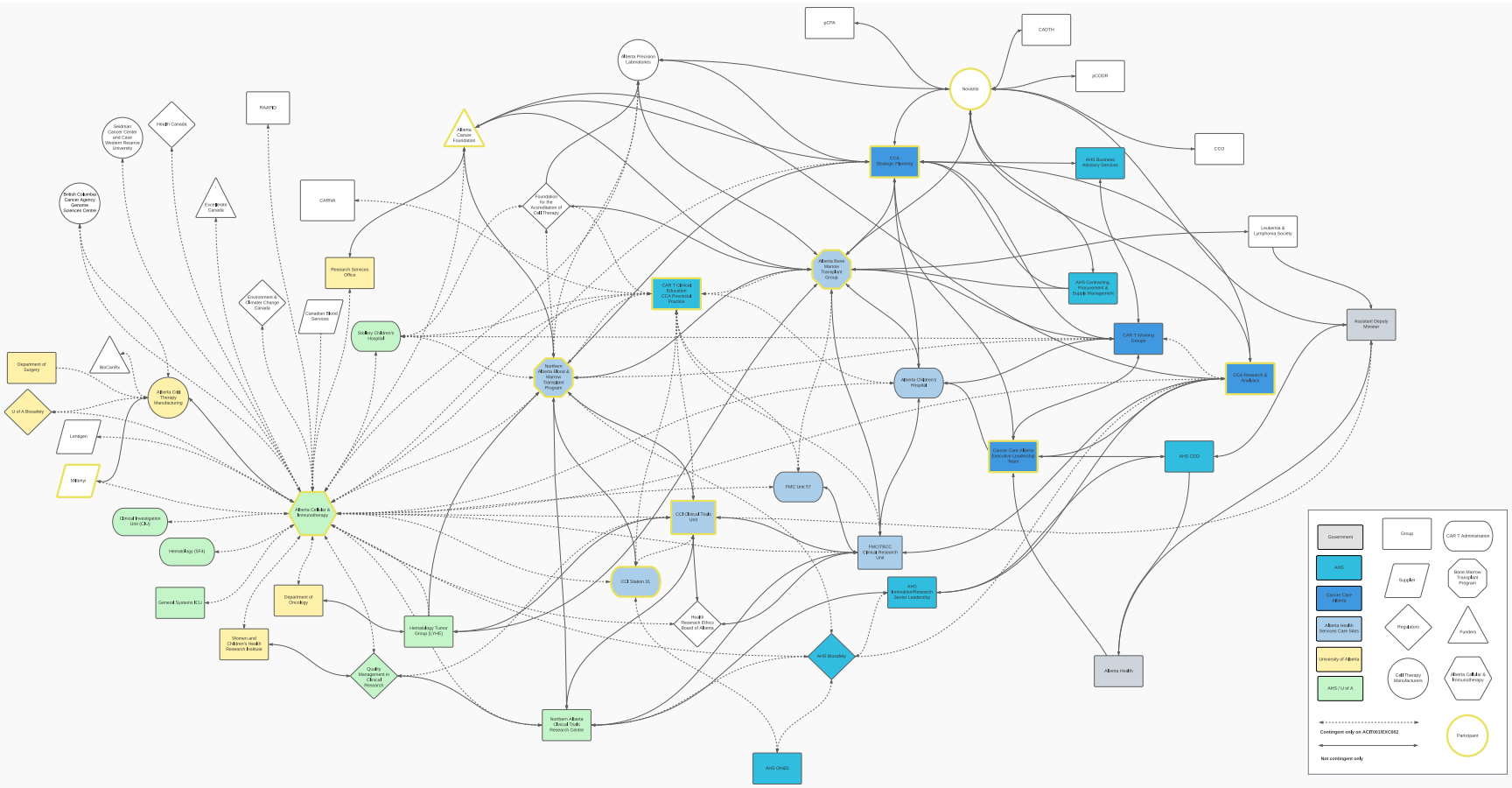

Figure 6. CAR T Adoption Stakeholder Network.

With increasing stakeholders also came opportunities and resources to re-invent the innovation, largely facilitated by ACIT, which connected vendors (i.e. Miltenyi, Lentigen and Canadian Blood Services) to the manufacturing and clinical research groups at the university; as well as the clinical programs (NABMT/ABMT) at AHS. Highlighted shapes denote interviewed participants, illustrating the extent to which stakeholder group was sampled in data collection. This network is broadly generalizable to any ecosystem that involves a specialized care delivery system (HCT), multiple clinical programs (ABMT/NAMBT), centralized health system management (CCA/AHS), and a clinical research component (ACIT, ACTM, NACTRC/QMCR).

ACIT001/EXC002 IIT

After securing U of A support to sponsor the study, ACIT and NABMT progressed toward an Edmonton CAR T program while CCA developed the business case. In 2019, the made headway in 1) constructing a CAR T manufacturing process that would merge optimally with the clinical infrastructure, 2) finding solutions to the study sponsorship and launch issues, 3) identifying and addressing operational challenges and 4) communicating Edmonton's resource needs to those developing the business case.

Prior to beginning local manufacturing, among other things ACIT needed to acquire reagents from the vector manufacturer, Lentigen, who would only provide them after an executed clinical trial research services agreement (CTRSA) between the sponsor of the clinical trial (University of Alberta) and the company was available. Negotiation of the agreement had been ongoing since December of 2018, and was stuck in a series of legal deadlocks [iii] by the second quarter of 2019; the sponsor (U of A) acting through the Northern Alberta Clinical Trials Research Centre (NACTRC) legal department (a joint AHS/U of A partnership) wished to ensure the product was not a biosafety risk to patients or employees and wouldn't sign off on the research agreement until this assurance was met. How that would happen was not clear as in April, after prodding by the ACIT PM, the NACTRC director admitted there were no established policies, guidelines, or training for biosafety risk level 2 (or 3) drugs in clinical trials-- and that they would need to establish those things before signing the CTRSA. To do so, NACTRC and AHS organized the 'AHS Biosafety Strategic Planning for Clinical Trials' meeting on June 27, 2021.

At this point, the PI responded with growing concern that new delays would impact patient survival and that the manufacturing process had "already met multiple biosafety approvals in academic health institutions across Europe and North America, not to mention health authorities in Canada, with the Victoria-Ottawa (VO) group currently screening their first patient" (Email, P14). The PI further recommend reaching out to the VO team to borrow standards and practices. Nothing came of that and the next biosafety related event was the aforementioned meeting at the end of June.

[iii] A deadlock is a situation in which no member of some group of entities can proceed because each waits for another member, including itself, to take action.

According to AHS and NACTRC, the purpose of the meeting was threefold: 1) to define the risk group level of ACT-C01, 2) to select an authority to review ACT-C01 and other theoretical RG2+ pathogens, and 3) to establish an AHS biosafety review process for clinical trials. During the meeting, the PI confirmed that upon completion of drug manufacturing at the ACTM (which holds a valid biosafety license for risk group 2 pathogens and whose biosafety officer had approved the manufacture of ACT-C01), the product would be considered RG1, as it was replication incompetent as determined by release testing and vector testing by the manufacturer.

Doubling down on their position, NACTRC and AHS directors passed off the responsibility of reviewing the project to an interim biosafety officer (iBSO) further delaying the project into August. With the CTRSA still unexecuted, the study team an alternative and managed to execute one of several material transfer agreements facilitating import of vector from the manufacturer Lentigen in Maryland to break the deadlock. With materials finally in hand, the initial development run was successfully completed yielding the first batch of Made-in-Alberta clinical grade CAR T cells in September 2019. The iBSO completed the initial review of the manufacturing process and clinical trial concluding that more information was necessary despite previous approval from the University of Alberta for the duration of the study. In their brief, the iBSO provided a 'Limited-Scope Institutional Approval', allowing for what they deemed to be missed documentation on manufacturing to be generated for further review. Regrettably, with patients begin to queue for enrollment onto the clinical trial, it would be another 18 months before the first patient could be treated with ACT-C01 due to federal and institutional approvals and the arduous process of securing additional clinical funding mentioned earlier.

Out-of-Province and -Country Access Options

Ontario and Quebec have been and remain the front-runners in Canadian immune effector cell therapy research and are much further along the adoption timeline of CAR T than Alberta and the other western provinces. Due to prior investments in infrastructure and championship in clinical

and basic science research, both provinces had a centre of excellence, which Novartis had selected to participate in a previous CAR T clinical trial, with a state-of-the-art federally-subsidized cell therapy laboratory. Like Alberta, during 2019, these sites had been preparing their institutions to introduce CAR T, but their governments and health administration had began arranging funds for their respective programs much earlier. By October 2019, with Alberta in the middle of developing its clinical funding request to the government, Quebec had already submitted their funding request, completed the review process, listed the drug on RAMQ (Quebec Board of Health Insurance), and received an annual governmental commitment of $35 million dollars[29] for their program. With that, they could treat an estimated 60 adults and 10 children pediatric patients per year and were ready to provide care, having already received their site certifications at Centre hospitalier universitaire (CHU) Sainte-Justine and Maisonneuve-Rosemont Hospital (HMR) in October.

In Ontario, the Juravinski Hospital in Hamilton funded Kymriah in May 2019 as part of a $25 million dollar BMT upgrade, which included clinical funding for CAR T infrastructure[30]. SickKids also received $12.5 million from the provincial government in May to revitalize the SickKids BMT/CT Unit[31], which was expected to reach completion within two years. By December 2019, Ontario had launched the Ontario CAR T-cell Therapy Program providing interim access for their patients in all three indications through preferred provider arrangements with three U.S. facilities[32] after having received their official certifications from Novartis for their local sites[33].

With standard of care CAR T now imminently available in other provinces, a CCI medical oncologist began attempting to send patients out-of-country to receive the therapy:

> *"I originally applied for a particular patient to head to the States before any of those [Canadian] sites were actually up and running. Just because obviously with Health Canada approval, I have to give access to my patients when their funding structure is available yet or not."(P14)*

During 2019, only two patients received CAR T in the US, and one received therapy in Ontario. The first patient to be sent away was referred from the CCI to the Mayo clinic in August 2019:

> *"I was unfortunately given a bit of a runaround with a request for further information upon further information upon further information over the span of about four months actually for that original patient, and I got nowhere fast. By that point, it became somewhat pointless for the patient to head stateside as it would probably become too financially difficult for them, simply because they had so many other medical issues going on that were a direct consequence of progression of their disease." (P14)*

Patient 1 was then referred to the Juravinski Hospital in Hamilton in the summer of 2020, after receiving treatment for now relapsed disease through another clinical trial at the CCI. The referral was refused by the Juravinski as there was no "reciprocal funding arrangement between the provinces" and "already had extensive wait times"[iv]. Another participant from a different Alberta site encountered the same challenges due to the absence of an agreement between provinces:

> *"So it was provincial funding. So Alberta would have had to reimburse Ontario for any of the costs that's including the product, but also clinical care. So the inpatient nurse, inpatient time, nursing time, any of the additional medications, investigations and tocilizumab if needed." (P14)*

From the time Alberta oncologists had identified access to CAR T in the spring of 2018 as a major priority to late 2019, it was estimated that "40-50 patients would have been eligible to receive the treatment" however, we only found evidence of four patients receiving treatment out of province (2 from Edmonton and 2 from Calgary) until CAR T was made available in Alberta". With poor results sending patients elsewhere during 2019, it was no surprise that the list of patients waiting for the Made-in-Alberta clinical trial to launch began to grow.

[iv] In October 2020 patient 1 was accepted by the Princess Margaret Hospital in Toronto which had found a way to temporarily cover the cost, but was unfortunately delayed due to COVID related infrastructure issues at PMH and was unable to receive the therapy until they were accepted onto the ACIT001/EXC002 as the third patient in 2021. The other Edmonton patient was referred in August 2020 to the PMH and received CAR T in late October 2020.

Implementation II: Re-Structuring

January 2020 – March 2021

Summary

The second implementation period was a time of peak activity in most stakeholder groups. ACIT completed manufacturing process development and secured federal regulatory approval for the study, while finalizing logistical and practical issues in conjunction with NABMT who also submitted the application for HCT FACT accreditation. During quarters three and four, Novartis worked with the APL CTL and ABMT to finalize their SOPs as well. In the health systems administration sphere, the grant was approved by Alberta Health and funding announced in August and procurement contracts were signed in December 2021. Final institutional preparations took place in February and March at each site and the CTPs were delivered as discussed in the final section.

ACIT001/EXC002

Acutely aware of the growing list of patients waiting to receive CAR T elsewhere, ACIT raced to receive regulatory approval and open the trial in 2020, through the height of the COVID-19 pandemic. In January 2020, they received preliminary ethics approval from the Health Research Ethics Board of Alberta (HREBA), pending Health Canada approval by a No Objection Letter. A second development run was completed in February 2020, and pre-CTA (clinical trial application) meeting was a month later in which Health Canada approved the manufacturing process, development/validation strategy and regulatory plan for multicenter manufacturing. Shortly thereafter, a university-wide shutdown halted manufacturing progress at ACTM. ACIT and ACTM management secured an exemption from the university to re-open the facility; however, this delayed the first validation run until June 2020. The results from that run were analyzed and compared with the development runs, and a second and final validation run was scheduled for and completed in September. After these results were received and analyzed, the ACIT PM completed the regulatory submission to Environment and Climate Change Canada (ECCC) in September. The Alberta Cancer Foundation then provided full approval and transferred the remaining funds to the research account of the study in November 2020. The ACIT PM mailed the CTA to Ottawa on December 4, 2020, and the No-objection Letter from Health Canada was received with minimal

recommendations by the PI on January 8, 2021, within the 30-day review window purported by Health Canada.

Business Case Review

After submission of the business case in January 2020, clinicians were in the dark as to the progress of the review:

> *"You know, once we submitted it to our higher ups, who then submitted it on our behalf to Alberta Health… that submission process [was] not clear cut. In other words, I was never clear as to who actually clicked send on the email, for example, there's no application portal or anything like that, which made it very clear that your application had been sent. The review process is entirely opaque and took the better part of eight to nine months before we even heard that this was just going to get approved." (P14)*

With Ontario and Quebec already offering standard of care CAR T, by mid-summer without any updates, physicians in Alberta were becoming frustrated. One began to apply pressure on the ministry through personal connections:

> *"So I'm on record saying that now, my wife worked for the government of Alberta, and because of those connections, I was able to meet with various deputy ministers and push this forward relating to innovation and also some of the resources. So I told them that there were people dying. I kept it simple. There were people dying. There was a new treatment that would work, but it would be a half million US for every patient. We had to buy it and we could do it for fifty thousand dollars, at the Cross per patient. But they had to help. We had to push from above. So I was able to use my wife's connections and get some political support from the Ministry of Health." (P3)*

Without any update on the status of the review, oncologists with terminal patients waiting for therapy began to look at other options:

> *"So I ended up sending two of my CAR-T patients to the US to get CAR-T in March and April and May, June, that kind of area, because I was done with it, I'm like, I was I was not having it... I can't wait any longer. Right? And so we started getting we started, um, recruiting pressure from the Leukemia Lymphoma Society. We wanted some help." (P2)*

Even with political pressure from high level physicians, the review process remained opaque and stagnant. In July, the responsible oncologists met and drafted a letter to the minister:

> *"I was at the cottage, so it was July 2020. You know, we still hadn't heard anything about the business case. So we had a meeting. I think [person] was there and drafted a letter to go up, you know, go to the minister to say, you know, what's up with this? What's the holdup? And I understand from my conversation with the minister that he also had been receiving pressure from parents of children with ALL. And so at the announcement, He said, what did he say? He said, you know, I've been I've been hearing about these CAR T-cell things, you know, from parents of sick children for a few months. And I spoke to my deputy and said, can we get this thing going in Alberta? Can we do this? And the deputies said, well, that's what this is on your desk here. Sign that. And so, you know then the funding started to flow. And then I think these pediatric parents had sort of greased the wheels along the way."(P8)*

One month later, in late August 2020, AHS announced the release of funds from the business case in Calgary in a hastily organized press conference. The major clinical contributor to the business case in Edmonton noted the approval stage of the review was equally inappropriate:

"…to this day, I actually don't even have an email that says you are approved. It literally was a notification by email from an AHS project manager saying that we're good to go and that there was going to be a press conference about 10 days after that I was given notice of it. And to that point, that press conference was actually in Calgary, and I actually wasn't even invited until the day before to participate in it. Not that I really needed to do so, but just recognition of effort was what I was looking for there."(P14)

In October 2020, the CTPOC met for the first time to discuss their next steps after the funding announcement. The conversation focused on delivery processes and procedures at TBCC and co-opting the (Alberta Bone and Marrow Transplant (ABMT) referral process for CAR T. A lack of physical space at TBCC for accommodating CAR T patients was also raised as an issue. Guidelines on rules for admitting and treating patients on the hematology unit of FMC were created and commercial product onboarding was reported to be ongoing during October with a Novartis audit and physician training.

In the industry sphere, the funding announcement in August triggered contract negotiations with AHS Contracting, Purchasing, and Supply Management (CPSM). Novartis also conducted a privacy assessment and lab audit of APL for cell handling during the third quarter of 2020. The contract for procurement of Kymriah was executed on December 31st, 2020. Despite a generally prolonged implementation process, this portion was very quickly and efficiently done, according to an industry representative:

"It was literally New Year's Eve, and I was walking around in the snow when I got the call that that, you know, the people like. And honestly, the team, the team at AHS, they were they were working through Christmas on this just like I was. So our global teams were as well. So. And the reason we did that was because they had patients they wanted to line up for January. And so it was a pretty big deal to have that all set to go because again, it's, you know, you can't do some of the other things until that stuff happens."(P13)

In fall 2020, CCA began parsing out the business case funds into functional centres, and in November, the Novartis audit had been completed, and Calgary sites were able to recruit new temporary FTEs.

Institutional Preparation

Excited frontline staff at both sites aware of the decision to adopt CAR T translated into the development of standard operating procedures (SOP) in early 2019, after the bifurcation into IIT and SOC pathways. Consequently, sites had almost two years to put develop their procedures and train staff. Procedure development in Edmonton was a joint effort led by the BMT team in pursuit of FACT accreditation and the ACIT team prior to launch of ACIT001/EXC002. At the CCI, new pathways and procedures were created, tested and implemented to facilitate delivery of ACT-C01. Screening and referral, apheresis, LDC regimens, CTP transport, CTP dispensing, administration, provision of rescue medications, and inpatient and outpatient monitoring and outpatient follow-up procedures were either adapted from H

CT or created. The apheresis and CTP transport SOP in particular were developed using parts of procedures in use in Calgary and kindly made available by ABMT/APL. Administration SOPs were drafted by ACIT to suit the needs of ACTM and NABMT, with the FACT PM adapting them for adherence to the appropriate FACT requirements. Inpatient monitoring and follow-up procedures were drafted by ACIT in line with the clinical trial protocol and utilized some of the documentation previously employed for the monitoring of immune related adverse events experienced by BiTE patients under previous clinical trials. Independently, a nursing educator at the CCI developed teaching materials for RNs on management of CAR T patients with ABMT and ACIT input between December 2020 and March 2021. Both sites reported that participation in previous BiTE trials and had enabled staff to become familiar with monitoring, recognition of and effective treatment of T-cell based immunotherapy side effects. Staff felt more comfortable with implementing CAR T because of this, stressing the importance of participation in clinical research. As expected, ABMT had a more developed CT program with SOPs for much of the above;

however, they had to work with Novartis to adapt these processes, which began at the site certification meeting in June 2020.

After the first wave of COVID-19 receded in the spring of 2021, uncertainty over the future impact on the UAH capacity mounted, and the Hematology unit providing inpatient after care levied pressure to move the trial back to the CCI. In response, the IIT PI and BMT physicians presented a proposal to CCI administration to change the site of CAR T administration from the UAH Clinical investigation unit (CIU) to Station 31 of the CCI in early February 2021. Inpatient nursing staff had been trained on the monitoring of CAR T patients over the winter, and after a translation of the administration SOP back to the CCI, several senior inpatient RNs were chosen to be trained on administration of ACT-C01. Physicians and other staff were trained at one of two site-initiation visits on trial specific details. As the product is preferably administered fresh, the procedure is much simpler than that of a cryopreserved autologous HSC product and doesn't require cardiac monitoring due to the lack of the cryopreservative dimethyl sulfoxide (DMSO) in the final formulation. Within two months after the decision to move the site, the CCI was prepared to provide care for CAR T patients. Final notifications and training were performed for staff and the first of two site initiation visits occurred on February 8th, 2021. Shortly thereafter, the CTRSA was signed and full administrative approval from AHS was received.

Implementation III: Clarifying & Routinizing

March 21 2021 - November 2021

Summary

Edmonton and Calgary sites launched their programs in March 2021 and began treating the patients who had accrued during the pandemic at a pace of one per month at each site over the first six months. The leadership met to review the preliminary data in November 2021. The next steps proposed by each group were the expansion of indications into mantle cell lymphoma and a move to an outpatient program. Hospital management expected significant attrition in the human resources resulting from the stress of the pandemic. Accurate assessment of the costs of the program was impeded by lack of clear system due to the novel mechanism of grant-funding for clinical costs and

late involvement by CCI CTU. Patients who received CAR T and survived relayed their perspectives to frontline clinical staff during or after treatment.

Program Launch

Initial treatments of anti-CD19 CAR T cell therapy in Alberta took place in March 2021, one week apart in Edmonton and Calgary. Unit 57 at the Foothills Medical Centre administered the first dose of anti-CD19 CAR T in the province; Kymriah on March 22, 2019[5]. NABMT/ACIT administered the second CAR T product (ACT-C01) to a patient in Edmonton a week later. The opening of both programs nearly simultaneously was synergistic in that patients not meeting the criteria for standard of care (i.e. adult ALL patients) could be treated on trial, and overflow patients in Edmonton not able to receive treatment on the trial could be treated by ABMT.

The manufacturing capacity of the ACTM limited ACIT001/EXC002 to the treatment of one patient per month. Regulatory restrictions imposed by Health Canada on early phase trials also limited early enrollment in ACIT001/EXC002 to seven patients in the first six months. ABMT was able to treat only two more patients within the first six months of the program, with an average vein-to-vein time of 33 days (versus a 14-day vein-to-vein time in ACIT001/EXC002). At the time of the interviews, both programs were operational but nascent in their experience. In each centre physicians and managers noted their biggest issue was human resources related to staffing:

> *"Well, I, you know, all so far, I wouldn't say that the resources, the funding isn't the issue. It's translating that funding into actual bodies. Our biggest problem right now that we're facing, which you've probably already heard about is the apheresis, you know, and we recognize this. We put it in the business plan. They bought us a new apheresis machine. Right. Like that was part of the business plan. And yet we're still we can't fit it in. Because we're still from a nursing and resource perspective, unable to deliver and proceed with apheresis, OBP has not allowed us to specifically designate areas for CAR-T." (P2)*

[5] The first dose of Yescarta (axicabtagene ciloleucel) was administered March 29, 2022. Personal communication, ABMTP Director, 2021.

"Like I said, I think the biggest funding need is going to be at that staffing level. I think in terms of supplies because it isn't a departure from the autologous collections that we're already doing and we can kind of incorporate that, especially if we're reducing some of the autologous transplants or collections that we're having to do. I think the biggest potential roadblock that we're going to run into and who knows what that looks like post-pandemic in terms of staffing levels, that's going to be potentially be the biggest roadblock. And I think that that's going to transcend nursing as well and go into your other health care professionals as well, right? Your physicians, hematologist, all those pieces." (P9)

The NABMT program also underwent their first FACT inspection in mid-August. Initial reports were positive and they expect to receive accreditation approval in early 2022.

CCA leadership reported that the grant funding structure through the business case allowed for tracking of patient outcomes and resource utilization. Clinical outcomes were presented to the committee in late November 2021 with promising results.

"…it all really depends on how this Made-in-Alberta thing goes, right? I think that's going to be a game changer for us if the Made-in-Alberta product is actually proven to be an effective alternative and that we can produce CAR-T locally." (P2)

Patient Perspective

According to the clinical trial nurse caring for the first six CAR T patients in Edmonton, patients found the experience of CAR T easier to tolerate than an autologous transplant and that they would consider that modality again, rather than a second transplant.

"So patients usually just say, you know, their side effect profile is quite different than what they were expecting. So, you know, they said they feel like it's a really, really bad flu. So I think that they were expecting more. So the people who had

gone through stem cell transplant before, whether it's auto or allo, they were expecting to feel like that where they said it's quite different." (P7)

"A few, most of the patients usually say that they would go through it again, that it wasn't as bad as they expected... It's not like a transplant where sometimes, say the myeloma as they go for, they can do a double transplant there, like some of the patients are just like, No, I'm not doing that ever again, and they refuse." (P7)

Patients also reported that they felt lucky to be part of the trial, given the limited spaces available, and that the therapy was available in Edmonton. Physicians remarked that they were also happy to be able to provide CAR T in Edmonton and compared it to the attrition seen for patients unable to receive allogeneic transplants through ABMT.

Next Steps

Transition to an outpatient based program was suggested in Edmonton through the IIT following the successful transition by American centres[34]. Indication expansion into second line therapy for relapsed disease post R-CHOP was also under consideration at the time of interviews in the autumn of 2021. To the first point, ACIT submitted a request to AHS innovation for reallocation of funding from the inpatient functional centre to pay for temperature monitoring devices to ensure early detection of CRS in the community. The proposal required was refused by CCA leadership citing difficulty in utilizing grant funds for capital expenditure despite availability of significant funds. Nevertheless, ACIT continued preclinical process development and validation at APL in Calgary and planned for expansion into SCH and TBCC in 2022. Unsurprisingly, these milestones are contingent on the recognition and further support of the individuals who drove implementation at each site, particularly in Edmonton.

Discussion

The timeliness of adoption is an important measure of the success of the innovation diffusion process. It is especially so in the case of CAR T given the unmet need. Here, we discuss the how

these events compare to analogs in other provinces and interacted to impact the time to delivery. In the next chapter, we will discuss all the other challenges and enablers at play as they relate to the other implementation outcomes.

During initiation, several decisions were made that influenced the adoption process (Figure 8). First, the clinical community recognized the therapeutic benefit of CAR T. Second, it advocated adoption of the technology through a joint meeting with CCA leadership remarkably early in comparison to other provinces. The multi-stakeholder format allowed voices from each centre to be heard and the meeting took place prior to market authorization. This showed foresight by the administration and clinical communities given the lack of interest in Alberta by cell therapy developers compared to centres in Ontario and Quebec. Of note, the role of the CCA leadership in facilitating this process is unique to the four Western provinces, all of which have a single provincial cancer agency that controls clinical funding, unlike hospitals in Ontario and Quebec that are individually funded and managed.

During the agenda-setting and matching processes between these stakeholders, the important challenges to adoption were acknowledged and informed two crucial decisions made by the administration: the therapy should be provided at both major centres due to the clinical interest and size of the unmet need, and that research into the development of a locally manufactured version should be undertaken and implemented in Edmonton first to build their infrastructure. With the administrative decision to pursue adoption, implementation formally began, and responsibility for driving implementation was handed over to clinical champions who volunteered to lead the development of the provincial program and implementation at their respective centres.

At this point in the narrative, an initial inconsistency arises-- the impetus for the business case. Through document analysis, it was ascertained that there was a directive to pursue clinical funding in the form of a business case at the Red Deer meeting. However, during interviews, one of the participants stated only after they were turned away by a FMC hospital administrator did the development of the business case occur. From this, we can surmise a single hospital administrator played a pivotal role in the early implementation process by refusing the in-kind

contribution of additional services to the program. It seems reasonable that without this individual the clinical champion may have been able to proceed with implementation without the CCA-advised business case.

Importantly, the business case provided an opportunity for a lagging Edmonton program to request (if not attain) additional resources and re-structure their program to fit the innovation. It also afforded them time to pursue FACT accreditation, which would help with eventually acquiring a commercial product. However, with the clinical funding ask ongoing in Calgary, NABMT and the Edmonton clinical community still had an enormous challenge in the lack of a CTL to contend with and significant unmet need. They began solving this problem at LYHE 2018 when the IIT was first proposed, effectively re-inventing[6] the innovation. The approach was pioneered by collaboration between American academic centres and cell therapy vendors from Europe, and had demonstrated feasibility at multiple sites in pediatric B-ALL and NHL[21,22]. Some of the benefits included a 75% reduction in price, half the time from apheresis to re-infusion, a CTP with more stem-like characteristics and possibility better persistence, ability to infuse a second dose at no cost, and administration of a fresh instead of a cryopreserved product.

[6] The innovation itself was actually improved and is significantly different than Kymriah. The word re-structuring here is used in the context of Rogers Diffusion of Innovations framework.

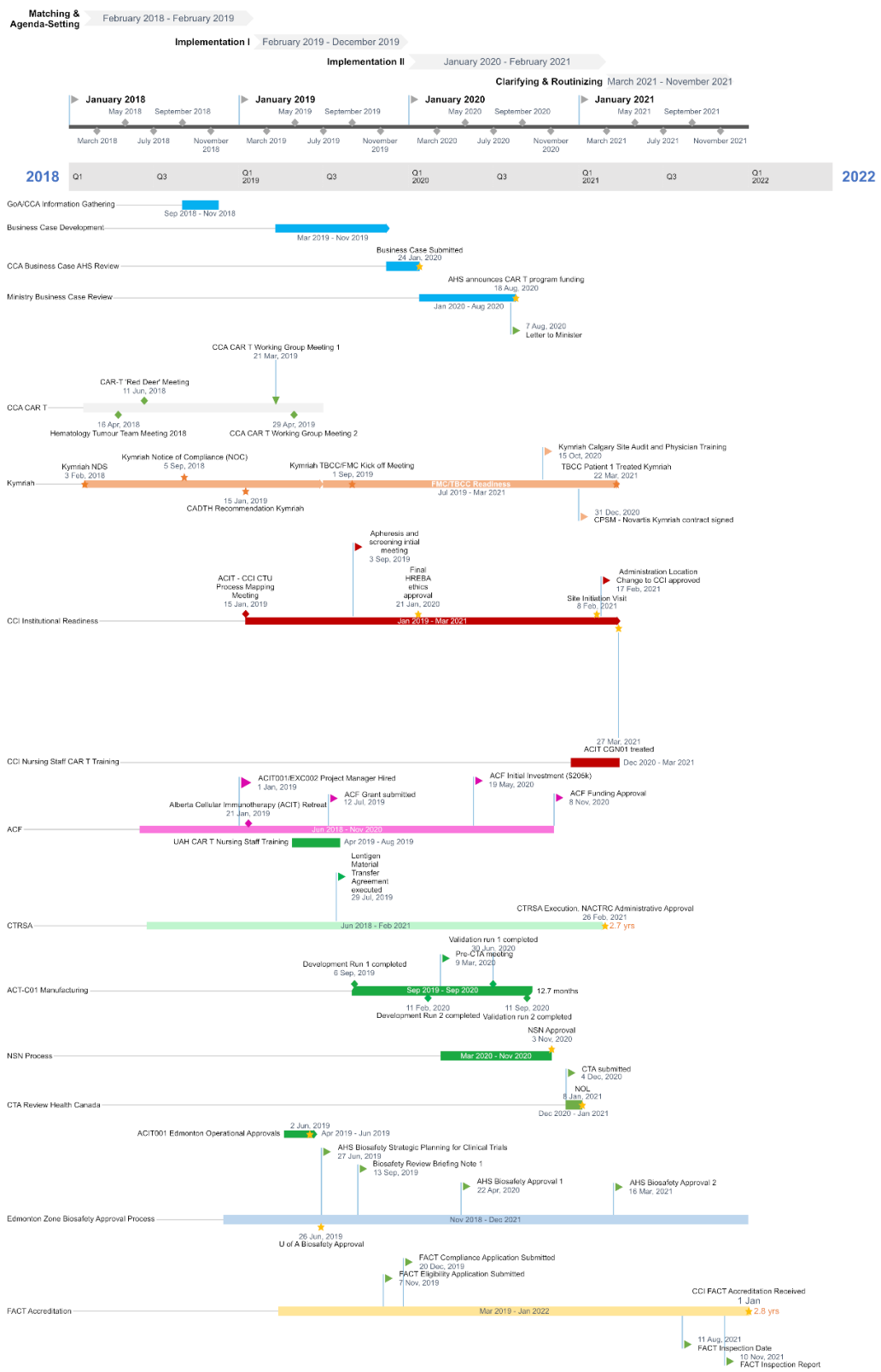

Figure 7. CAR T Adoption Timeline

During the reviews by AHS and government, providers began to refer patients out of country and province for CAR T with limited success. With government approval of the funding proposition, Novartis re-engaged the Calgary centre to undertake institutional preparations. Driven by the magnitude of unmet need in 2020, ACIT finalized the ACT-C01 manufacturing process, received regulatory approvals and finished cell therapy related standard operating procedures at the CCI. During this period, the COVID-19 pandemic and concurrent implementation of the EPIC digital health system competed with the adoption process for staff and clinical resources.

In March of 2021, both two anti-CD19 CAR T products were delivered to the first patients in Alberta. The groups would each go on to treat similar numbers of patients through the first year and begin to assess the outcomes of the program. Cost monitoring systems were developed, initial results collected and optimization possibilities discussed in late 2021.

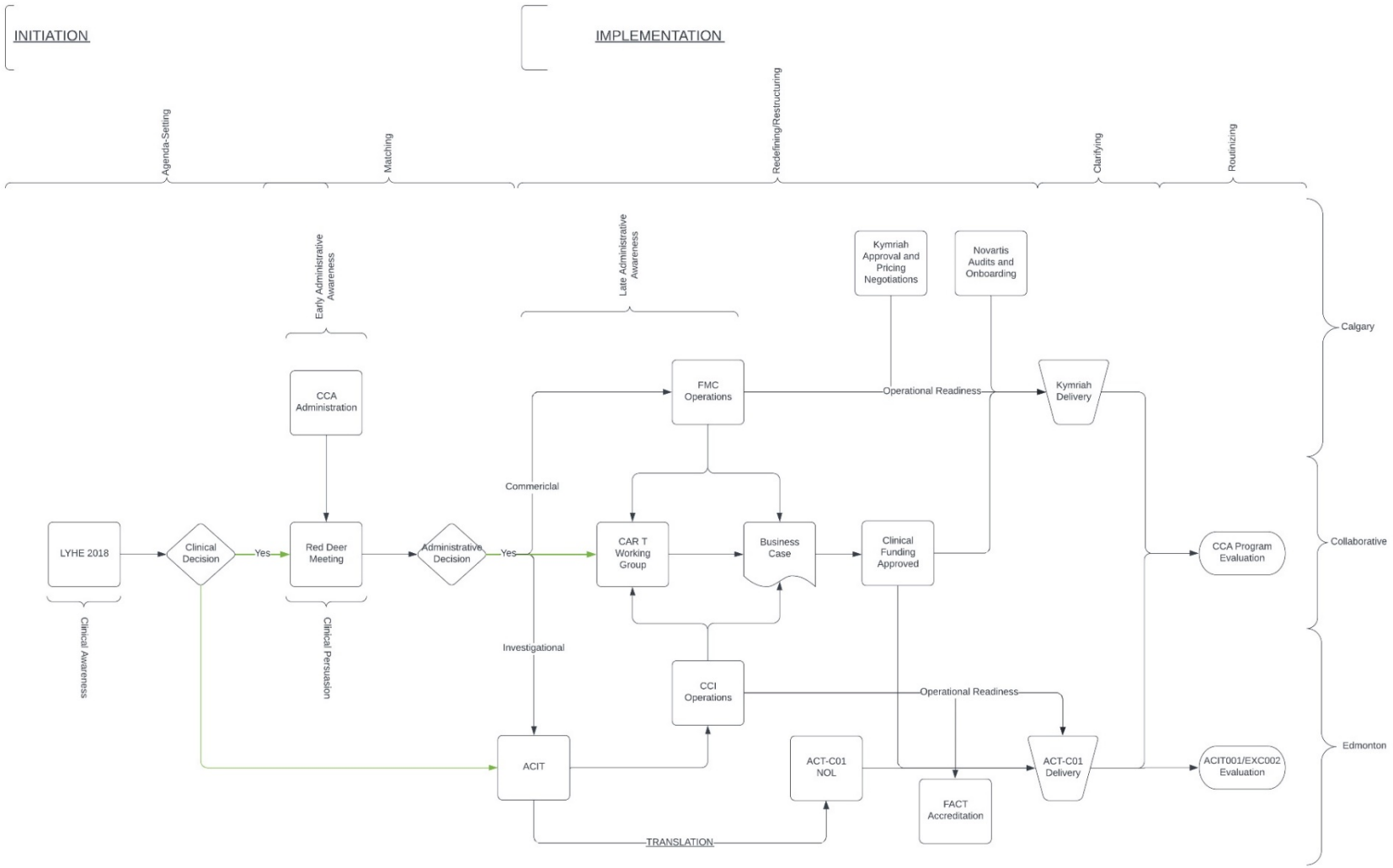

Figure 8. CAR T Adoption Process

General schematic of the key events and process in the adoption process used to parse the timeline into the stages of diffusion along the x-axis and by clinical site along the y-axis. Some overlapping between matching and agenda-setting stages was observed when clinicians and administrators at the Red Deer Meeting. Also of note, the initial evidence of innovation restructuring took place during the initiation stage, with the clinical decision leading to the formation of ACIT, suggesting that these processes may incept prior to implementation, and begin earlier than outlined in Rogers' model.

Research Team and Reflexivity

The primary author conducted each interview as part of their MSc thesis research, which also included an historical review of the clinical adoption of CAR T. During the time of the study, they were employed by Cancer Care Alberta, Cancer Research & Analytics as a project manager of the clinical trial ACIT001/EXC002 (NCT03938987) and were one of the two initial members of Alberta Cellular and Immunotherapy (ACIT). The primary author has work and experience in a clinical oncology research specializing in lymphoid hemato-oncology. Prior to this study, they had worked as an inpatient unit clerk at one of the study sites from 2008-2014 while completing a BSc in Biological Sciences. Additionally, the author contributed to original research on the global clinical translation of cell therapies. The interviewer had also previously conducted and participated in other qualitative research studies that included interviews, and had been trained in these methods in the School of Public Health at the University of Alberta. Eleven of fourteen interviewees were acquaintances or colleagues of the author prior to the study. Due to the author's proximity to the unmet need in this population, they come from a position of advocate for CAR T implementation.

Limitations

This study was limited by a lack of information available on the final price of Kymriah or the arrangements made by governments to pay for it as neither are not publicly disclosed. Government stakeholders were contacted for participation but declined. As such, it is unclear to us at what point key decisions were made at the government and provincial payer levels, however some of that ambiguity was mitigated by acquisition of interview data from industry participants involved in negotiations.

Conclusion

CAR T is a relatively expensive and complex modality, however it yields considerable clinical outcomes in an expanding number of indications (many of which had never seen meaningful prognostic improvement). There is also a dearth of literature on the real world adoption of patient-specific CTPs, especially in publicly-funded healthcare systems. We hypothesized that an

incompletely known list of factors influenced the manner in which CAR T was adopted in the province of Alberta. Some of these we expected to be at play based on previous literature were the perceived complexity of the intervention, existing hospital characteristics/infrastructure, and the high cost of the treatment. We expected their combined effects could be estimated objectively through the time to provision (compared to other provinces) and subjectively through the accounts of stakeholders in the process. Lastly, we thought that providers at sites with less developed infrastructure would be forced to advocate to a greater extent for access to treatment on behalf of their patients, and at a larger scale we might see evidence of these factors affecting implementation, service and client outcomes including access to therapy for patients.

To test this hypothesis, we undertook a historical review approach we identified salient events processes and constructed a timeline of events comprising the adoption process. We aggregated the stakeholders involved in these activities and presented them in a network providing an example of how the ecosystem currently functions when confronted with an innovation. Using interviews, the timeline data was validated and supplemented where necessary, and partitioned according to Roger's theory of implementation in an organization to discern the challenges and facilitators at play during each phase of the process.

CAR T was adopted by and implemented in Alberta over a roughly four-year period. It was made available to patients in the form of two different CTPs (ACT-C01 and Kymriah) each at a unique clinical site. The clinical community, industry, philanthropic organizations, universities, health system and hospital administration were all involved in the process. Compared to Ontario and Quebec, Alberta lagged behind in terms of time to delivery. Relative to the rest of the provinces however, Alberta has been able to adopt CAR T quickly, given that sites in other provinces are still in the process of developing programs.

Site specifically, the most time-consuming processes in Calgary were related to the business case, and in Edmonton were related to legal challenges, regulatory review and manufacturing process development. Foreseeing these delays, ACIT began to develop the MIA CAR T program early in 2018 and successfully translated a comparator into the clinic in slightly over three years. As a result of the step-wise approach Novartis chose to roll out the technology, and without t the clinical

trial support from ACF addressing multiple implementation issues at the CCI, we conject that at present, CAR T would only be available through ABMT. At that point, with indications expanding, undue strain would have been placed on that facility creating more infrastructure and cost challenges in the future for clinicians and administrators. Fortunately both centres adopted CAR T; the NABMT was able to secure FACT accreditation for their HCT program through the process, get access to CAR T therapy for patients to prepare for IEC accreditation, as well as build new relationships with a potential partner for cell processing in the future. ABMT continued to grow its apheresis/CTL infrastructure and human resources through the business case and is well poised to continue its leadership in the field. Concurrent, salient events that impacted the process were the COVID-19 pandemic and the rollout of the digital EMR EPIC at both sites.

In the next chapter, we discuss the challenges and enablers to the adoption process and how they formed and interacted to produce the timeline we have constructed. Each site undertook institutional preparations individually (but with evidence of informal knowledge transfer) and these were not a significant contributor to time from adoption to delivery, or a major concern for the clinical community or hospital administration.

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Appendix 1.1: Data Extraction Template

#	Type	Event Date	Date Range	Source	Title	Ownership	Author(s)	Organization(s)	Source (Primary/ Secondary)	Outcomes	Decisions	Decision Impact	Quotes to use (with page number)	Commercial/ Academic/Both	Notes
1	Meeting Minutes	16-Apr-18	N/A	AHS	HEMATOLOGY TUMOUR TEAM MEETING (LYHE 2018)	AHS	N/A	GURU	P	Identification of CAR T and recognition of value--acknowledged as being "soon standard of care"	Schedule meeting of stakeholders	Red Deer CAR-T meeting scheduled	"CAR-T Cell Therapy is an emerging therapy for NHL ,B-ALL, myeloma, and other malignancies, and will soon be standard of care" (pg. 5)	Both	None

Appendix 1.2: Master Interview Guide

Focusing Questions

1. What was your role in the introduction of CAR T in Alberta/clinical site?
2. What were the key challenges specific to this type of therapy?
3. How does the introduction of CAR T differ when compared to the introduction of other innovative technologies in oncology?
4. How did the differential infrastructure and past experiences in Edmonton and Calgary impact the introduction of CAR T in Alberta?
5. What were some of the successes in the implementation of CAR T in Alberta, and how do you think the implementation process could have been improved for future technologies?
6. What role did the business case play in the introduction of CAR T?
7. What pathway did the business case follow after it's submission to Alberta Health?
8. How was the decision made to pursue implementation of commercial product in Calgary and Academic product in Edmonton?
9. How did the following factors affect this decision:
    a. Accreditation status
    b. HSCT programs
    c. Selection by sponsors
    d. AHS leadership decision making
    e. CTL for product handling and prep
    f. Role of pharmacy
10. How did there come to be an IIT and commercial product implemented nearly simultaneously?
11. What additional infrastructure was required to implement CAR T in a research and commercial context at the TBCC?
12. Could you describe any collaboration between other sites in the implementation process?
13. Which tasks were shared and which were unique to each trajectory?
14. How did these factors interact to produce timeline for each trajectory?
15. What are the results on final process and outcomes of each approach?

16. How could the implementation process have been improved to better serve Alberta patients?
17. What were the major challenges to implementation of each product and CAR T in general?

External Factors

18. Fludarabine shortage
19. COVID-19
    a. University shutdown of manufacturing prior to VR1 and VR2
    b. Miltenyi tech to perform software update delayed
    c. Health Canada CTA review time period extended
    d. UAH ICU constraints
20. EPIC/Connect Care
21. Human resources

Clinical Trials/Development

22. What is the status of implementation of commercial CAR T products at the TBCC?
23. What is the level of access to CAR T for ALL and NHL for Alberta patients currently
24. Are you able to send patients to other centres to receive this therapy?
25. As a center that has prepared for CAR T implementation what was required in terms of infrastructure, SOPs and could you outline these tasks in order they were completed?
26. How does FACT accreditation influence the process of CAR T implementation?
27. Having now provided CAR T at the TBCC under a clinical trial, has there been an increase in resource utilization? Which services or departments were affected most?

Clinical Factors

28. What do you expect the future indications of CAR T for NHL and ALL will look like
29. Are there any delivery or implementation issues that you anticipate are unique to Alberta or Edmonton?
30. To what extent will the delivery of chimeric antigen receptor T-cell therapy require additional staff or training?

31. What would be an ideal system to manage outpatients who have responded to the therapy, but could still experience toxicities?
32. How have the unique side-effects associated with chimeric antigen receptor T-cell therapy affected the implementation of these products at the (site)?

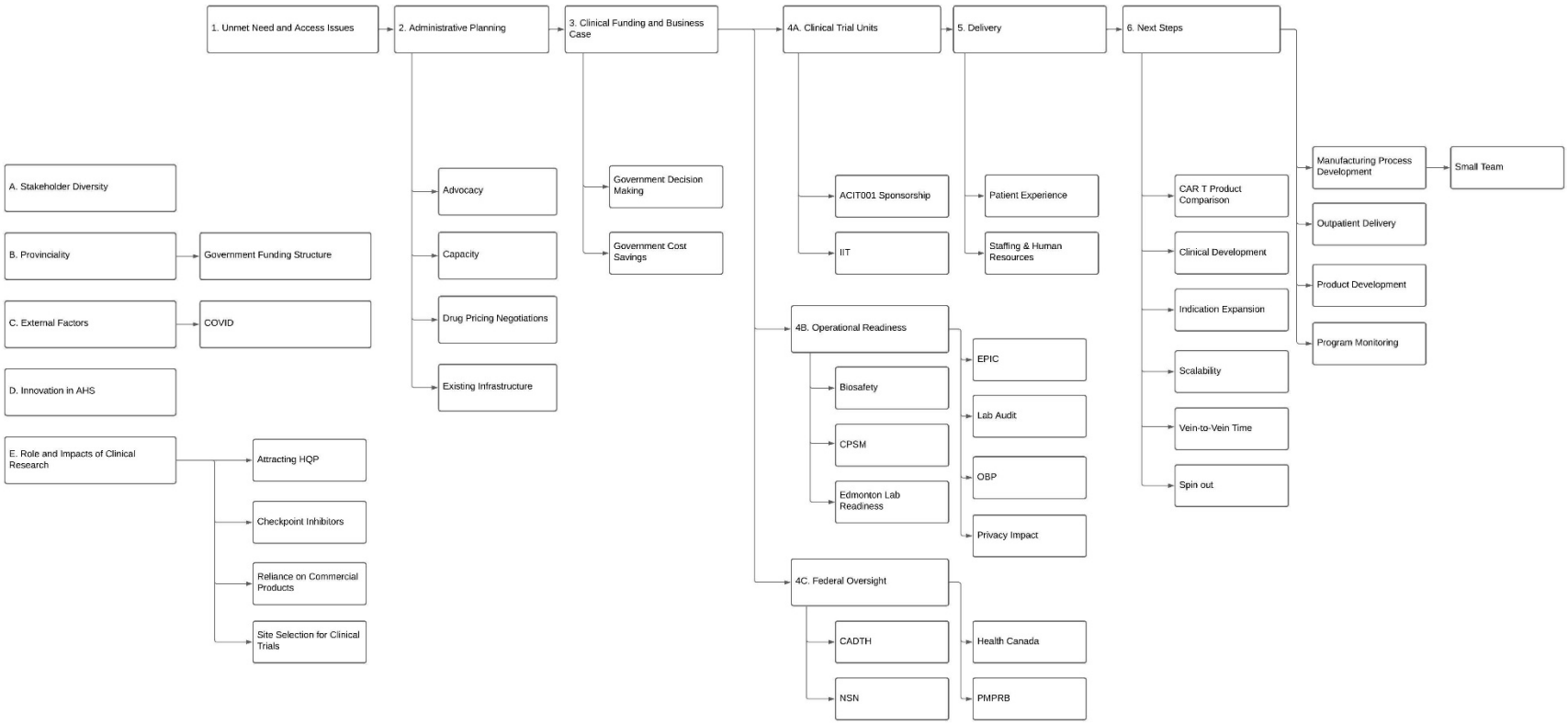
Value Assessment/Funding/Policy

33. Experience with the business case and were those resources sufficient
34. If chimeric antigen receptor T-cell therapies are reimbursed using a leasing model or performance based pricing structure what party should gather effectiveness data, and how should this information be collected?
35. How has the AHS leadership perception of CAR T changed prior to and after implementation?
36. What is planned in terms of monitoring the CAR T program in Alberta going forward?
37. How was the governance structure for CAR T implementation chosen and has it been successful in its goals?

Miscellaneous

Do you know of any individuals that have expertise on any of the topics above that would be willing to participate in this study?

Appendix 1.3: Coding Tree



Chapter 3: A Retrospective Comparative Case Study of the Challenges and Facilitators Encountered during the Clinical Adoption of anti-CD19 CAR T-cell Therapy in Alberta

Background

Researchers studying the translation continuum[1,2] of cell therapy[3–5] describe challenges/barriers and facilitators/enablers to the path a technology takes from development to routine use. For CAR T in particular[6–11], literature spans the life cycle of the technology, from the acquisition of research funding[12], clinical translation[13,14], manufacturing[15–19], implementation[20,21], clinical trial design and conduct[22], regulation[23], to commercialization[11,24,25], reimbursement[26], and pharmacovigilance/surveillance[27]. With several years elapsed since initial market approvals, the literature borne out of clinical trials has given way to published research on the practical challenges of adopting CAR T, initially addressing the implications for hospital services and clinical specialities: laboratory[28], apheresis[29–32], community oncology[33], nursing[34], pharmacy[35,36], hematology[37], neurology[38], pathology[39] and radiology[40]. Reviews notwithstanding, a dearth of published literature exists on the concerted challenges faced during real world case studies of CAR T implementation[21,41,42]. A better understanding of the challenges to the adoption process and the lessons learned could help to refine current practices and contribute to better outcomes when implementing and developing new health technologies[43].

Presently, there is no published literature evaluating the implementation or adoption of a cell therapy with an implementation science framework; something which provides researchers with information on the factors that can affect the implementation process of different innovations, enabling them to collect and analyze data from the field in a reproducible, comprehensive and consistent way. After an initial survey of potential frameworks, the author selected the Consolidated Framework for Implementation Research (CFIR), which has been utilized to gain an in-depth understanding of the factors impacting the success or failure of the implementation of behavioral and non-invasive interventions (i.e. screening programmes, healthcare delivery policies/programs)[44,45]. The CFIR has been well established in the literature as tool to assess

implementation of various interventions, and has the capacity to accurately record and present the factors I hypothesized as influencing the adoption process of CAR T: product cost and logistical complexity[5]; individual/group perceptions and motivations in decision-making and communication networks; the prior conditions of the adopting clinical site(s)[21]; and lastly, the impact of innovation characteristics like magnitude of improvement of existing interventions[46]. The CFIR was also the most detailed framework compared to other potential frameworks for complex interventions[47].

Domain 1: Intervention – characteristics of the intervention itself
• Intervention source: Perception about whether intervention is externally or internally developed • Evidence Strength & Quality: Perception of the quality and validity of evidence supporting the belief that the intervention will have desired outcomes • Relative Advantage: Perception of the advantage of implementing the intervention versus an alternative solution • Adaptability: Degree to which an intervention can be tailored to meet the needs of an organization • Trialability: Ability to test the intervention on a small scale, and to reverse course if warranted • Complexity: Perceived difficulty of implementation • Design Quality & Packaging: Perceived excellence in how the intervention is bundled and presented • Cost: Cost of the intervention and costs associated with implementing the intervention
Domain 2: Outer Setting – factors external to the organization
• Patient Needs & Resources: Extent to which patient needs are accurately known and prioritized by the organization • Cosmopolitanism: Level of connectedness and networks with other organizations • Peer Pressure: Competitive pressure to implement an intervention • External Policy & Incentives: external strategies to spread interventions, including policy and regulations, mandates, recommendations and guidelines, etc.
Domain 3: Inner Setting - characteristics of the organization implementing the intervention
• Structural characteristics: Age, maturity, or size of the organization • Networks & Communication: Nature and quality of webs of social networks and the nature and quality of formal and informal communications within an organization • Culture: Norms, values, and basic assumptions of a given organization • Implementation climate: Relative priority of implementing the current intervention versus other competing priorities • Readiness for Implementation: Access to resources, knowledge, and information about the intervention
Domain 4: Individuals - characteristics of the individuals involved in implementation
• Knowledge and Beliefs about Intervention: Individual staff knowledge and attitude towards the intervention • Self-efficacy: An individual's belief in their capabilities to execute the implementation • Individual State of Change: Phase an individual is in as he or she progresses toward skilled, enthusiastic, and sustained use of the intervention • Individual Identification with Organization: Individuals' perception of the organization and their relationship and degree of commitment to the organization • Other Personal Attributes: Personal traits such as tolerance of ambiguity, intellectual ability, motivation, etc.
Domain 5: Process – processes of implementation
• Planning: Planning for the implementation • Engaging: Engaging individuals in implementation processes • Executing: Executing the implementation plan • Reflecting & Evaluating: Reflecting and evaluating the progress of implementation

Table 1. Consolidated Framework for Implementation Research Domains and Constructs

Clinical adoption of CAR T in Alberta comprised translation and implementation of an investigational (decentralized manufacturing at point-of-care) CAR T product; and implementation only of a commercial (centrally manufactured and cryopreserved) CAR T product; each at a unique clinical site. Herein, the challenges and facilitators (C/F) are defined as any factors that could impact implementation, service, or client outcomes[43] (Appendix 1.4).

The adoption of CAR T in Alberta included implementation of an investigational product developed in-house. The C/F associated with preclinical development and manufacturing are beyond the scope of this thesis and already covered comprehensively in the peer-reviewed literature[17–19,48,49], so the extent to which they are considered is intentionally limited. C/F unique to the clinical development of ACT-C01 (i.e. not applicable to the implementation of a commercial product at the same site) were flagged for future analysis and fit to a CFIR construct despite being more traditional translational challenges or facilitators generally faced first by CTP developers[50]. Early stage clinical translation is often driven at least in part by a clinical investigator operating within an academic hospital setting, and is subject to social C/F like perceptions/motivations related to funding, management, risk etc., which are captured by the CFIR.

The objectives of this chapter are to:

1. Identify the key ideas, challenges to and facilitators of the adoption of CAR T in Alberta,
2. Analyze and present the results using the Consolidated Framework for Implementation Research and evaluate it's suitability in the context of CAR T,
3. Discuss the success of implementation by established implementation outcomes[43], and suggest lessons learned and recommendations for similar technologies.

Methods

Research Question

This study was performed to answer the following questions:

1) What factors affected the success of the clinical adoption of CAR T in Alberta?
2) What lessons can be learned to optimize the adoption and implementation of CAR T and similar innovations in the future?

Ethics Approval

The research project of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Challenges of and Enablers to Implementation of Adoptive Lymphocyte Therapy", No. Pro00064788, on June 14, 2016.

Innovation Definition

In this study, the innovation is defined as anti-CD19 4-1BB zeta CAR T cell therapy (herein referred to as CAR T). Of note, at each site, a different version of this innovation was implemented (tisagenlecleucel at Southern Site, and ACT-C01 at Northern Site). ACT-C01 and tisagenlecleucel are both 3rd generation autologous CAR T products containing the same co-stimulatory domain but differ in other critical aspects related to the CAR design, starting material, transduction methods, culture conditions, quality testing procedures and formulation. Therefore, ACT-C01 may be thought of as a later iteration of anti-CD19 CAR T therapy arising from further development in manufacturing method.

Study Setting

Alberta is a province containing two cities of roughly the same population, each with a tertiary cancer centre (clinical site) that together service the HCT needs of the majority of Western Canada including Alberta, Northwest Territories, Saskatchewan and non-lower mainland British Columbia. The Foothills Medical Centre and Tom Baker Cancer Centre (FMC/TBCC) are considered a single clinical site/case in Calgary, as are the University of Alberta Hospital and Cross Cancer Institute (UAH/CCI) in Edmonton. The sites are now both over fifty years old, opening two years apart in 1966 (FMC/TBCC)[51] and 1968 (UAH/CCI)[52].

Calgary (Southern) Site Infrastructure

With the decision to base allogenic transplants in Calgary in the late 1970s, FMC/TBCC became the preeminent bone marrow transplant medicine center in the province, doing their first autologous transplant in 1980[53], allogeneic transplant in 1983, and becoming FACT accredited in 2006[vii]. The site received a significant upgrade to their clinical infrastructure in 2011, with $78 million to replace the bone marrow transplant unit and expand inpatient services[54]. HCT graft processing is performed at the Cell Therapy Laboratory (CTL), a purpose-built facility in the FMC to service the ABMT program. The manufacturing and clinical infrastructure coupled a history of proactive leadership positioned the site well for the adoption of CAR T.

Edmonton (Northern) Site Infrastructure

Unlike the Tom Baker Cancer Centre which is located within the larger Foothills Medical Centre complex, with access to specialty care including neurology and critical services, the Cross Cancer Institute is a standalone facility (with access to a nearby tertiary care centre). The University of Alberta (U of A) substantially influenced the strategic directions of health research and care in Edmonton and is now the provincial centre of excellence in solid organ transplantation. To that end, government invested heavily in the infrastructure required to manufacture cell therapy products used in beta cell transplantation in Type I diabetes[55]; the centrepiece of which is the $26.2 million dollar Alberta Cell Therapy Manufacturing Facility (ACTM). The building was completed in 2014 with grant funds awarded at the federal, provincial and local level[56] (Canada Foundation for Innovation, Alberta Enterprise and Advanced Education and the University of Alberta), and is solely managed by the Department of Surgery in the Faculty of Medicine & Dentistry. It is cGMP compliant and provides contract manufacturing services and space for U of A research. As its mandate is primarily to facilitate University research, it is presently not a Foundation for the Accreditation of Cell Therapy (FACT) accredited facility.

[vii] Personal email communication (Calgary ABMT Medical Director and Unit Manager, 2022)

Regarding lab and apheresis services, the CCI recently re-acquired the capability to aphorise patients from Canadian Blood Services (CBS) in April 2018[viii], whereas the Calgary site utilizes the apheresis service of Nephrology at the FMC. Calgary, however, has the ability to store and process cell products (including HCT grafts) through their on-premises clinical lab, the Alberta Precision Labs Cell Therapy Lab (APL CTL), whereas the CCI, like smaller sites in Ontario, rely on CBS to fulfill those needs[57].

Study Design

A retrospective qualitative comparative case study design[58–60] was used to study the province-wide adoption of CAR T. By considering both sites, this method 1) maximized the probability of identifying all potential C/F; 2) enabled differential categorization of C/F into site-related and site-unrelated factors; 3) provided insight into how different iterations of the innovation itself impacted implementation, 4) enabled the comparison of the effect of means of provision (standard of care vs. investigational); and 5) captured the differential effects of centralized management decisions-making on a bicentric delivery model.

Sampling and Recruitment Strategy

Participants were recruited through purposive sampling. Specifically, they were identified during a historical review (chapter 2); from professional relationships between the author and some of the participants (through their role as a project manager of the locally manufactured CAR T clinical trial); and sampling during interviews where participants were asked at the end of the interviews if they had other potential participants to suggest. Potential interviewees were recruited through an email which was sent on August 18, 2021. Utilization of existing relationships with colleagues allowed the author and supervisory committee to secure the participation of high-profile interviewees including: the current and former directors (where applicable) of each BMT unit, an industry representative from the commercially implemented CTP, two high-level health system administration directors and a medical director of one of the adopting sites. Two potential interviewees (one government and one industry) declined involvement in the study because study participation was contrary to organizational policy.

[viii] Personal email communication (Edmonton NABMT Unit Manager, 2022)

Interview Guide

Based on professional experience in the adoption and implementation of CAR T, and academic experience in studying the clinical translation of cell therapy, the author developed a master interview guide with general and specific questions for the participants. After general questions were asked, questions from the relevant section of the interview guide were asked to the participant according to their stated roles and responsibilities and topics they touched on in their answers to the specific questions. The master interview guide is available in Appendix 1.1.

Data Collection

Data were gathered through 14 semi-structured interviews conducted over four months (August to November 2021). The author conducted each interview over either telephone or by Zoom. Median length for the interviews was of 43.5 minutes in length (range from 23 to 59 minutes). The organization to which each participant belongs was obtained but not included here to protect their anonymity.

Organization	Occupation	Title	Stakeholder Group	Length (min)	Participant #
1	Director	Research & Analytics	Health System	48	10
1	Director	Strategic Planning	Health System	32	5
2	Physician	BMT Director	Clinical/Institution	51	2
2	Physician	Former BMT Director	Clinical/Institution	49	8
3	Director/ Physician	Facility Medical Director/ Executive Leadership	Institution/Health System	40	6
3	Physician	Medical Oncologist	Clinical	58	14
3	Physician	BMT Director	Clinical/Institution	47	1
3	Director/ Physician	Former C(T/R)U Director	Institution	32	3
3	RN	Clinical Educator	Clinical/Institution	26	4
3	RN	Clinical Trial Nurse	Clinical	23	7
3	Manager	Nursing Manager	Clinical/Institution	20	9
4	Director	Director of Philanthropy	Funder	39	11
5	Manager	Medical Science Liaison	Industry	51	12
6	Manager	Patient Access	Industry	52	13

Table 2. Key Informant Demographic Information.

Acronyms: C (T/R) U: Clinical (Trial/Research) Unit, depending on site. CTU: Northern Site, CRU: Southern Site.

During interviews, interviewees were thanked for their participation, and informed consent was confirmed and verified (consent was reviewed for completion and verbal confirmation received prior to the initiation of interview). Participants were made aware that interviews would be recorded and could withdraw at any time prior to data analysis. The interviews started by asking participants to state their name and position, and describe their roles and responsibilities in relation to CAR T adoption in Alberta. This was followed with questions about the adoption timeline and an inquiry as to the C/F they were aware of regarding the implementation of CAR T in Alberta. Prior to completion of each interview, the interviewee was asked whether they could recommend other participants for the study or if they had anything else to add and were thanked again for participating. Interviews were recorded on an iPhone 6s using 'voice recorder', uploaded to a secure server, and transcribed using Sonix transcription services. The interview transcripts were reviewed on the Sonix platform by the author for errors and re-read several times.

Data Analysis

The author analyzed the data first inductively and then deductively using thematic analysis methods[61,62]. The author inductively coded interviews using NVivo software for C/F and key ideas relevant to the research question. As interviews were conducted, the author grouped coded data according to five key stages of the innovation process in an organization (agenda-setting, matching, redefining, clarifying, and routinizing)[63]. This approach was useful to help separate C/F acting at different points in the adoption process. For example, a statement regarding the lack of available clinical resources would be coded under chronological group two 'Administrative Planning', then theme 'Existing Infrastructure'. The author coded transcripts in an iterative fashion, recoding when necessary as the coding schema was refined (final coding tree is available in Appendix 1.3). After coding was finished, small sub-themes were collapsed under larger themes where necessary.

The unit of analysis used to determine thematic saturation was the clinical site. Saturation was reached after 9 interviews when the same key ideas began to appear in the subsequent interviews; however, due to the limited number of individuals involved in the planning of the

clinical implementation process and administrative leadership, the author proceeded with additional interviews to ensure no new information was missed. For site-specific roles where only one individual had sufficient knowledge to contribute (i.e. two person study team, including the author), themes were considered saturated as the entire population had theoretically been sampled.

Two additional researchers with extensive experience conducting research with qualitative methods[64,65] reviewed a sub-sample of interviews to confirm internal validity. They independently coded each interview and compared results to ensure agreement across individuals.

Although the CFIR framework fit our hypothesis, due to the novelty of the context in which it was used, the author collected and analyzed the data using an inductive approach initially to ensure no data was left out due to unforeseen limitations of the domains/constructs. To improve knowledge translation, the individual key ideas, challenges and facilitators were mapped onto the constructs of the consolidated framework for implementation research. This approach allows stakeholder groups to quickly and easily find the challenges and facilitators that are relevant to them (clinicians: inner setting, innovators: innovation characteristics, government/administration: process).

Results

Inductive Analysis

The challenges and facilitators identified during the inductive coding were grouped into five site-unrelated themes (stakeholder diversity, provincial approach, administrative structure, external factors, response to disruptive initiatives, role and impacts of clinical research, and unmet need/drug access) and nine site-related themes (advocacy, administrative planning, clinical trial units, operational readiness, federal regulatory approvals, delivery, and future considerations). In addition, some of the themes were developed by grouping one or more sub-themes. Site-related themes and sub-themes contained challenges and facilitators which were dependent on an aspect of the site and acted at specific points along the adoption timeline, whereas site-unrelated themes

and sub-themes contained challenges and facilitators were not conditional on site, and acted across broader periods of time during the adoption process. The C/F under each theme and subtheme are presented in Tables 3 and 4.

Site-Unrelated Themes

Step 1: Inductive Analysis			***Step 2: Deductive Analysis***
Themes	**Subthemes**	**Challenges and Facilitators**	**CFIR Domain and Constructs**
Stakeholder Diversity		Challenges • CAR T involved many individuals and groups in the process, each requiring sign-off for their areas especially across hospitals	Inner Setting>Networks & Communication Innovation Characteristics>Complexity
Provincial Approach		Facilitators • Engaged clinical staff existed at both sites • Funders supported the idea of local manufacturing for a cheaper, more cost-effective, treatment closer to home • Provincial nursing education approach provided resources to nascent center • Provincial approach by AHS/CCA allowed nascent sites to acquire infrastructure through a larger centre initiated request • Increased redundancy in services	Process>Engaging Inner Setting>Learning Climate Process>Planning Characteristics of Individuals>Knowledge & Beliefs about the Intervention Process>External Change Agents
Administrative Structure		Challenges • Resource silos of individual departments made comprehensive communication difficult • Multiple hospital department accounting made it difficult for management to see potential cost-savings on aggregate • Difficulty in relaying information from clinicians to administration • Existence of intermediary (Cancer Care Alberta) between government and hospitals (vs QC/ONT) causes delays from an industry perspective Facilitator • CCA intermediary developed a proposal (business case) for additional funding • ABMT not under direct supervision by or funded through Cancer Care Network, yielding flexibility	Inner Setting>Structural Characteristics Inner Setting>Available Resources Process>External Change Agents Process>Reflecting & Evaluating
External Factors	**COVID-19**	Challenges • Competed for resources at both clinical sites and prevented OOP referrals • Slowed federal regulatory reviews of ACIT001/EXC002 • Affected commercial rollout by impeding manufacturing and ability to audit sites	Process>External Change Agents Inner Setting>Available Resources
	Clinical Information System	Challenge • CAR T competed for time and human resources with the rollout of the clinical information system at the Northern site.	Process>External Change Agents Inner Setting>Available Resources

Step 1: Inductive Analysis			***Step 2: Deductive Analysis***
Themes	**Subthemes**	**Challenges and Facilitators**	**CFIR Domain and Constructs**
Role and Impacts of Clinical Research		Challenges • Increased burden on inpatient staff to perform clinical trial monitoring and more rigorous assessments • Tracking clinical trial costs was a novel challenge across multiple departments Facilitator • Cost savings from government perspective because of free drug under trials	Inner Setting>Implementation Climate Process>Engaging Process>Reflecting & Evaluating Innovation Characteristics>Cost
	Attracting HQP	Facilitator • Cutting edge research attracts and helps retain highly qualified personnel (HQP)	Process>Reflecting & Evaluating
	Relevant Clinical Experience	Facilitator • Both sites had institutional experience with immunotherapy (checkpoint inhibition and bi-specific T-cell engagers) which prepared clinical staff for managing CAR T patients	Innovation Characteristics>Adaptability
	Control over Implementation by Pharma	Challenge • Pharma controlled CAR T access in Canada during rollout and after implementation • Industry specified need for FACT accreditation precluded some centers from adopting CAR T early in the diffusion process • Pharma has company headquarters in Eastern Canada and work with those sites preferentially • Pharma early movers chose a sequential vs. simultaneous rollout model	Process>External Change Agents Process>External Change Agents Inner Setting>Available Resources Inner Setting>Structural Characteristics
Response to Disruptive Initiatives		Challenge • Inflexible and routinized culture of staff in hospitals and clinical trial/research/units groups Facilitators • Strong clinical trial data drove implementation • Determined clinical community	Process>Reflecting & Evaluating Inner Setting>Networks & Communication Innovation Characteristics>Evidence Strength & Quality Process>Engaging>Champions
Unmet Need/Drug Access		Challenges • Patients had to travel for treatment prior to clinical adoption in Alberta • Delays in access caused by governments negotiating funding arrangements Referring patients in a timely fashion to other centres	Innovation Characteristics>Relative Advantage Inner Setting>Structural Characteristics/Networks & Communications Inner Setting>Implementation Climate>Tension for Change Outer Setting>Implementation Climate>Cosmopolitanism

Table 3. Site-Unrelated Themes (Inductive/Deductive Thematic Analysis of Interview Data and Mapping to CFIR)

Site-Related Themes

Step 1: Inductive Analysis			***Step 2: Deductive Analysis***
Themes	**Subthemes**	**Challenges and Facilitators**	**CFIR Domain and Constructs**
Advocacy	**Philanthropic & Patient Group Advocacy**	Facilitator • Philanthropic and patient groups advanced the adoption process by lobbying government	Process>External Change Agents
	Disease Foundation	Facilitator • ACF funded clinical trial manufacturing costs and formally appointed implementation manager at the Northern site	Process>External Change Agents Process>Engaging>Formally Appointed Implementation Leaders
	Physician Advocacy	Facilitator • Clinical championship drove implementation	Process>Engaging>Formally Appointed Implementation Leaders
Administrative Planning	**Inpatient Capacity**	Challenges • Inpatient demand for CAR T was expected to outstrip CCI/FMC institutional capacity • Transplant patients already consume the majority of CCI inpatient bed resources Facilitator • Estimated resources required by clinicians expected to exceed that of a single centre, facilitating a multicenter approach	Inner Setting>Implementation Readiness>Available Resources Inner Setting>Structural Characteristics
	Business Case	Challenges • Multiple AHS departments and hospitals involved complicated development of the business case	Process>Executing Inner Setting>Networks & Communications
	Government Decision Making	Challenges • Clinicians had no clear pathway to propose potential cost-savings on to administration • Opaque and time-consuming review process • Difficulty engaging government	Process>Reflecting and Evaluating Process>Engaging
	Hospital and Lab Regulation	Facilitators • FACT accreditation enabled preferential selection of the site by pharma for rollout of commercial product • Clinical laboratory enabled transport, storage, and receipt of cell therapy products • Infrastructure and resources of the allogeneic transplant program at the Southern site, including SOPs, experience, physical infrastructure, accreditation status • Enabled manufacturing of cGMP CAR T locally • Clinical interest drove implementation	Process>External Change Agents Inner Setting>Structural Characteristics Inner Setting>Readiness for Implementation

Step 1: Inductive Analysis			***Step 2: Deductive Analysis***
Themes	**Subthemes**	**Challenges and Facilitators**	**CFIR Domain and Constructs**
Clinical Trial Units		Challenges • Perceived complexity and novelty of CAR T • CCI CTU unwilling to support or sponsor trial Facilitators • Homogenized CCI CTU structure at Northern site • Independent IIT program at Northern site • University and ACF provided funding, bridging the gap left by the CCI	Inner Setting>Culture Inner Setting>Leadership Engagement Innovation Characteristics>Perception of Source Process>External Change Agents
Operational Readiness		Facilitators • Institutional experience with similar products (BiTEs) enabled smooth implementation and buy-in from nursing • Pre-launch education programme made nurses more comfortable with the process • Similarity in delivery to auto-HCT • SOP development was enabled by external agents at both sites (other hospitals, FACT), contribution contingent on existing infrastructure Challenges • Novel burden on inpatient staff to monitor trial patients compared to SOC (Northern site)	Process>Executing Inner Setting>Implementation Climate>Learning Climate Innovation Characteristics>Adaptability Process>External Change Agents
	Lab Audit	Challenge • Lab audit performed virtually by Novartis (first ever for the company) due to COVID expedited implementation at southern site, with novelty leading to delays (Southern site)	Process>External Change Agents
	OBP	Challenge • AHS controlled spending through operational best practices to benchmark a program to others across Canada, and used this approach to incentivise the Southern site to cut spending before releasing further assets (Southern site)	Outer Setting> External Policy & Incentives
	Privacy Impact	Challenge • Privacy impact assessment performed by AHS to ensure that patient identifiers were not accessible through commercial cell tracking program (Southern site) Facilitator • Knowledgeable and experienced staff in contracts, supply and procurement and assessments of chain-of-custody and protection of patient information (Southern site)	Process>External Change Agents Process>Planning

Step 1: Inductive Analysis			***Step 2: Deductive Analysis***
Themes	**Subthemes**	**Challenges and Facilitators**	**CFIR Domain and Constructs**
	Biosafety	Challenge Institutional inexperience in development and delivery of viral vector transduced cell products (Northern site)	Innovation Characteristics>Perception of Source
Federal Regulatory Approvals	**Health Canada**	Challenge • Health Canada approval for the clinical was a significant contributor to the overall time to launch (Northern site)	Process>Executing
	Environment and Climate Change Canada	Challenge • ECCC NSN review was time consuming and unnecessary (Northern site)	Process>Executing
Delivery		Facilitators • Clinical staff at both sites competent in collection, infusion due to similarity of HCT • IIT allowed for policies and procedures to be revisited and adapted during implementation as needed yielding improved user satisfaction and trial integrity	Innovation Characteristics>Adaptability Inner Setting>Available Resources Process>Reflecting & Evaluating
	Patient Experience (proxy)	Facilitators • Patients reported the treatment process as smooth and that having a single point of contact in the trial setting as nice • Patients grateful to have a space on trial and that they can receive treatment closer to home	Process>Executing>Innovation Participants
	Staffing and HR	Challenge • Retention of staff post-pandemic as a challenge for the future Facilitators • Experienced and engaged clinical nurse educator was an asset • Improved clinical experience through delivery of CAR T	Process>Executing>Stakeholders Inner Setting>Implementation Climate>Learning Climate
Future Considerations		Facilitator • CAR T engaged health system leadership who are now committed to supporting the program grow	Process>Engaging Leadership
	Clinical Development	Facilitator • The flexibility of CAR T as a modality provided options for motivated investigators to develop their own products	Innovation Characteristics>Relative Advantage
	Indication Expansion	Facilitators • CAR T was expected to expand into other indications • CAR T was reported as a potential successor to HCT in second line NHL • Utility as a modality in other cancers and autoimmune conditions	Innovation Characteristics>Cost Innovation Characteristics>Relative Advantage Process>Reflecting & Evaluating

Step 1: Inductive Analysis			*Step 2: Deductive Analysis*
Themes	**Subthemes**	**Challenges and Facilitators**	**CFIR Domain and Constructs**
	Scalability	Challenge • Provision of CAR T commercially was impeded by global use of a single manufacturing facility in NJ and COVID	Process>External Change Agents
	Spin-out/ Commercialization	Facilitator • Potential cost-savings from commercializing ACT-C01	Process>Reflecting & Evaluating
	Small Team	Facilitator • Small research team facilitated expedient product development	Process>Reflecting & Evaluating
	Vein to Vein Time	Challenge • Longer vein-to-vein time contributes to worse patient outcomes	Innovation Characteristics>Relative Advantage
	Outpatient Delivery	Facilitator • Outpatient delivery relieved stress on hospitals and improved patient satisfaction	Process>Reflecting & Evaluating
	Program Monitoring	Facilitator • Monitoring of costs through the clinical trial and grant funding mechanism provided administration the ability to assess the level of success of the programs at each site	Process>Reflecting & Evaluating

Table 4. Site-Related Themes (Inductive/Deductive Thematic Analysis of Interview Data and Mapping to CFIR)

Site-Unrelated Themes

Site-unrelated themes are those which capture challenges and facilitators to adoption of CAR T that acted broadly over the process and without influence of site characteristics. These include external factors such as COVID-19 and C/F arising from third party groups like pharma, and the broader health system. Site-unrelated themes are a more generalizable group to other technologies and health systems, but do not offer the level of specificity to CAR T found in the site-related themes section.

Stakeholder Diversity

Stakeholder diversity captured the sentiments of participants who reported the increased diversity of stakeholder groups was a challenge to the adoption process. During the interviews, study participants stated that the complexity of CAR T and associated more diverse stakeholder involvement relative to other technologies and initiatives, slowed the adoption process. Examples of this phenomenon were the involvement of CCA and AHS administration during the development of the business case and the inclusion of U of A and NACTRC to bridge the gap left by the lack of internal clinical research support from CCI CTU.

> *"At least in my, my experience, [it was] a novel thing because you had collaboration between the foundation who put it a significant chunk of the money, the cancer program, the non-cancer health care system and government to be able to move this forward. I mean, that's incredibly complex and to try to get everybody to get on, get on side with that, that's what took so long... So I think that's probably the biggest thing. Now you have relationships and pathways and [you can] say something like this can be done and this is how we did it. So I think that's probably one of the big lessons." (P6)*

Provincial Approach

Provincial approach was a theme that included many facilitators to the adoption process. A provincial approach was defined as the propensity for individuals and groups to favor

harmonization and collaboration provincially or to consider and evaluate through a provincial lens.

> *"So the governance structure was actually proposed by the clinical leads in an earlier communication with leadership and the idea being that this would be a provincial project, not an Edmonton or Calgary project. And then what kind of structure did we need to move it forward provincially?" (P5)*

Taking a provincial approach was looked on favorably by funders and government, and allowed the site with less infrastructure to benefit from the work done at the more advanced site in terms of inclusion in the business case. It also added redundancy while programs were growing and allowed for knowledge to be shared between sites. Conversely, taking a provincial approach posed a challenge in that with an additional level of administration (CCA) between hospitals and government, the channels of communication are less direct and prone to misinterpretation. AHS as an organization was mentioned as averse to change generally and participants expressed frustration in trying to drive change from below.

> *"... there's little ability for that person to act on it or do anything but move it back up the chain, and eventually the message gets so diluted down to someone who has no clinical context, that either the reporter of this information or the receiver of the information has very little ability to act on it, so if you're three or four steps away from the person that's actually delivering the care, then it doesn't work that well. You need this sort of team of people whose job it is to really do this innovation to create-- be like the creator team and really, you know, break through the bureaucracy, really..." (P1)*

<u>Administrative Structure</u>

The theme of administrative structure captured challenges and facilitators stemming from the pre-existing structures of provincial health system to the level of the clinical program (i.e. HCT programs).

Siloing of resources across AHS was another challenge, making it difficult for implementation leaders to clearly communicate with all affected individuals and groups at once leading to confusion:

> *"…Cancer Care Alberta didn't own all of the pieces that were required to get CAR T cell therapy going in Alberta, and this was this was actually the big challenge. So [individual] might be right in that there was pushback from senior operations, people out, let's say, foothills or whatever. But that wasn't the impetus of the case… they had to be convinced to be involved in the business case because when Cancer Care Alberta said this is important, it's important for cancer treatment, it's important for people, then you've got other parts of AHS coming back and saying, well, that's great Cancer Care, but this impinges on our budget, so it impinges on our ICU budget, it impinges on where we provide apheresis, it impinges on that, how are you going to be sure that we are not going to end up having a hole in our budget because you want to do this novel treatment that involves centers outside of your tertiary cancer treatment centers?" (P10)*

Cancer Care Alberta functioning as an intermediary between government and hospitals helped facilitate acquisition of additional clinical resources through the creation of a business case:

> *"…it was because [individual A] and [individual B] so often we were in talking to the government people and then they came back and said, well, that's great cancer care, but we need a business case for this. So of course, the challenge is that putting the business case together, this is where Cancer Care Alberta could drive that, and somebody like [individual C] could do a lot of*

the work that she did with you guys in trying to get into shape that government would understand the government would accept." (P10)

The additional level of oversight did however come at an expense— participants at the Northern site found it difficult to relay important ideas back up the chain of command and refine their pathways of care:

"I mean, certainly on a site level, there's approvals there, but I suspect that because there's some funding change that would have to occur, that goes up to a provincial level through Alberta Health and eventually to the minister. But again, much like the business case it's entirely opaque as to how to make that happen. So temperature tracking, preventative medications such as Anakinra for IL-1 inhibition, tighter managing over the weekends. You know, having a 24/7 touchdown space, being able to give tocilizumab on the drop of a hat at any time of the day as an outpatient again delivery, given that it's only a one hour infusion. All of those are things that we could easily do to keep people out of hospital, but things that aren't easily done at this point in time." (P14)

How each site was managed was mentioned as facilitating or challenging implementation. Participants discussing the Southern site where the program is funded and overseen through the hospital and not CCA—found that structure allowed for better "flexibility" in the approach compared to the Northern site.

"Dr. Russell, in the past had really built himself a nice program with both the inpatient portion and outpatient process as well, or program as well from the foothills and the Tom Baker, respectively. He did a masterstroke really in creating the program the way he did, because there's a lot more flexibility, if it's unable to be offered in one there's a potential of it being offered in the other." (P1)

One drawback to that structure is that ABMT is more reliant on the in-hospital nephrology service for their apheresis needs as well as the general FMC infrastructure.

> *"There's other apheresis procedures out there. Nephrology is a big user, nephrology. Because all of apheresis procedures, the ECP, [(extracorporeal phototherapy)] we're doing that right. Edmonton's not doing ECP."*

From an industry perspective, having an intermediary group (like Cancer Care Alberta) between hospitals and government added a layer of administrative oversight that challenged adoption compared to other provinces like Ontario and Quebec where government funds hospitals directly.

> *"So the in western Canada, all four western provinces have a central funding agency for cancer products. And so to do something there, you have to get funds that are very dedicated to cancer. And so it's very specific and the budgets are very specific and they're managed tightly. And so that's what we had to work through here. And so on the one hand, it's a very tight system in cancer they have all the metrics and everything in a place like Quebec in Ontario, you know, they're they fund it differently and it's funded to different hospitals. So we see this with other drug funding. They will list something, but some of the implementation stuff isn't actually necessarily ready to go." (P14)*

External Factors

Two sub-themes (COVID-19 and Clinical Information System) were combined to form the theme of external factors. Each sub-theme corresponded to a challenge identified during interviews: the concurrent rollout of a new clinical information system (Connect Care), and the COVID-19 pandemic. The clinical information system was reported as a challenge by participants from the Northern site mainly due to its novelty, as neither the UAH nor CCI had

translated oncology workflows into a digital form before. The pandemic had knock-on effects across many areas; according to industry, it forced much of the accreditation and auditing process online, which proved to be a challenge due to its novelty. However, given the efficiencies found in conducting these evaluations online, the company opted to routinize the practice:

> *"And I don't know if you remember back to at that time, COVID was just rampant in in New Jersey, so there was nobody coming in. You couldn't even come here. So and Alberta would not want anybody from there coming in either. So. So that was it was, you know, for us, it is a pretty, pretty big deal getting, you know, doing that type of thing. And now that's going to be something that we will make as a best practice because it's just not realistic to go to every site. Like you say, there's no reason why you can't walk around with a camera and say, send us these readings, you know, show us your SOPs…" (P13)*

COVID-19 also posed a major challenge to manufacturers that relied on a large number of staff working in a single centralized facility to produce commercial CAR T product by forcing management to rapidly implement systems to manage spread among works and potential product contamination. The pandemic also slowed regulatory review of the ACIT001/EXC002 clinical trial, which affected adoption at the Northern site in particular. In hospital, COVID forced a competition for clinical resources and put additional strain on human resources at both sites, causing a change of delivery hospital at the Northern site only months before program launch.

> *"…even in midstream we had to change because with COVID-- the University Hospital didn't have the ICU capacity and didn't have the inpatient capacity to look after these patients, so we moved a lot of that to the Cross. In fact, almost everything is done here. It's only if the patient runs into trouble, they go to university hospital. So we've had to adjust on the fly…" (P14)*

Across the country it had similar effects and prevented out-of-province referrals to CAR T prior to availability in Alberta due to pandemic-strained hospitals in Eastern Canada.

> *"By the time that I got up and running, Toronto had been added on as extra site for Novartis product, and ideally it actually had just launched as well. So I attempted to send her to Toronto that got sidelined for a combination of COVID outbreak, but as well as because of the funding being not clear yet there too. But in fairness, COVID did play a part." (P14)*

Role and Impacts of Clinical Research

Several interviewees mentioned the challenges to and facilitators that institutions encounter when participating in or sponsoring their own institutional clinical trials. Participating in clinical trials as an institution can be a challenge, as it puts increased burden on clinical staff in terms of additional monitoring and documentation required by regulators and sponsors, a challenge at the Northern site specifically, which prior to ACIT001/EXC002 had never conducted clinical trials with inpatients, and as a result had no method for moving data from there to the clinical trials unit. However, provision under clinical trial did confer accounting benefits because all associated clinical events (imaging, bloodwork) were tracked by trial identifiers on requisitions, which was not the case at the Southern site where CAR T was provided as standard of care. Providing drugs under clinical trials also confers cost-savings for governments, as the cost of the drug is covered by the trial sponsor, making investment in clinical research programs attractive for government because they end up saving money, especially with expensive drugs like CAR T. This understanding was cemented through CAR T, as reported by a hospital administrator, which in turn fostered support for the business case in government and executive level administration.

> *"I think it's also highlighted the value of doing these clinical trials because if I'm government now saying, well, this is what it's going to cost the standard of care. But if we support Edmonton and Calgary in opening this through a clinical trial, we don't pay for the product. We can do all the other stuff with. That product itself costs $300-$400,000, so there's a significant saving to the*

system where that money could be redeployed. And I think that's probably been an eye opener for people in government. We've been trying to tell that from just standard drug savings for years and finally they're started to listen. But this, I think they got the message loud and clear is $400,000 drugs that if we do it through a trial, we get for nothing. We just need to put all these other things in place that we would have been doing anyway, giving the standard of care drug. So I think it's highlighted to lots of people who really didn't haven't seen that the value of doing a lot of these things through trials in terms of the cost saving, but also we're moving things forward." (P6)

Several sub-themes were also developed within this theme such as attracting highly qualified personnel (HQP), relevant clinical experience, and control over implementation by pharma. Two of these subthemes contained facilitators to adoption and sustainability of CAR T which were, the attraction of HQP wanting to work with these innovative products, and the accumulation of clinical experience by existing staff who would then help grow and promote the program. Another subtheme was developed to capture the unique challenges that came from the control pharma had over the implementation process. A major challenge within this subtheme was how pharma selected sites for clinical trials; they chose to select more developed sites first, usually from large centres in Ontario and Quebec, inadvertently exacerbating the site-to-site infrastructure and human resources inequality westward across the country.

"I think the thought was that they just needed to take it to a couple centers and have them highly competent. And they needed proximity, I think, to where our cell manufacturing was, which was down in New Jersey. And so because if you were coming all the way to western Canada, you're adding a day or two and that can present extra logistics. So that's my sense of why they picked those sites. It wasn't anything to do with clinicians, of course, because there's lots of, you know, world expertise in any of the western provinces as well. So it wasn't a reflection on that at all. I think it was being realistic that they might be spreading themselves too thin." (P13)

Furthermore, sites needing to be FACT accredited prior to implementation posed a challenge to the Northern site. As the accreditation requirement was one mandated by industry, the clinical trial was able to provide CAR T initially, providing an opportunity to treat several initial patients, a condition which enabled eventual FACT accreditation, helping breaking the institution out of this cycle.

> *"I mean, I think Calgary was picked one hundred percent because they were already FACT accredited. So that is full stop what it was. We made a concerted effort to first go to accredited again because we knew we had really high thresholds for lab audits and things. So it doesn't have anything to do with because I know some of our competitors don't need that need or ask for it. And again, we feel that we can relax that now that we're in major accredited sites, but our preference is still that they're fact accredited. So that's where we knew the Edmonton was going to be. And we said, well, you know, why don't we just work with them? And maybe the two things will happen around the same time."*

Response to Disruptive Initiatives

The final site-unrelated theme pertains to how the organization dealt with change and called 'response to disruptive initiatives'. C/F that described the institutional attitudes toward innovation and change were captured under this theme. Participants noted a challenge to adoption in the culture of reticence to accepting change, especially at the administrator level. Opposing this challenge under this theme however, was strong clinical trial data was as a facilitator helping to overcome institutional barriers when coupled with determined clinicians.

> *"But I would say that the ground that we've broken and the methodology, I guess, if you will, to try to get up and running starting from a viral vector that has established some clinical data to then actually going through the translation process and starting is something that I think others can follow. I think we've established the utility of it to Alberta Health and Alberta Health Services, and I think that Alberta Cancer Foundation sees the merit and the*

benefits of seeing products like this come to fruition. So definitely, I think that there's a lot more confidence in doing something in Alberta for cell therapies and innovative medicines. Have we figured all the infrastructure and all the method of getting open? Not quite. I suspect that there's a few hurdles there that will now come up after we've established things." (P14)

Unmet Need and Drug Access

The clinical community stated there was difficulty referring out-of-country prior to availability of CART T locally, of CAR T as standard of care. Out-of-province referrals were also delayed by a lack of reciprocal funding arrangements between provinces to cover costs. For patients who were accepted by other institutions during this period, they had to travel, which was difficult due to their condition. Clinicians also reported that poorer outcomes were common for patients traveling to receive care for allogeneic transplants, a similar treatment.

"I was unfortunately given a bit of a runaround with a request for further information upon further information upon further information over the span of about four months, actually for that original patient and I got nowhere fast. By that point, it became somewhat pointless for the patient to head stateside. As it would probably become too financially difficult for them, simply because they had so many other medical issues going on that were a direct consequence of progression of their disease. So I attempted to send that patient to, Hamilton instead, to receive Novartis product. I was told that the wait times for that were quite extensive." (P14)

Site-Related Themes

This group of themes captured challenges and facilitators specific to a site, because of: a) the unique characteristics of each site (i.e. existing infrastructure), b) factors related to the product adopted at each site (tisagenlecleucel vs. ACT-C01), c) the mode of provision (clinical trial vs. standard of care), or d) site-specific decision making or human resources. Themes were arranged in chronological order based on where in the adoption process they acted as described by

interviewees beginning with challenges associated with unmet need, followed by access challenges prior to adoption and concluding with future considerations described by participants after implementation.

Advocacy

Two participant groups (clinicians and philanthropy) advocated for access to the drug in order to facilitate and expedite adoption of CAR T in the province. Disease foundations played a significant role in facilitating access at the Northern site where they supported clinicians in acquiring new human resources to lead implementation from within and financed manufacturing of locally-produced CAR T, while another disease foundations lobbied government for approval of the business case at the Southern site later in the adoption process. One disease foundation that supported the IIT reported that local access and manufacturing and cost-effectiveness were positive aspects for funders. The clinical community drove implementation at both sites, playing a major role in coordinating resources, planning for future needs and communicating between stakeholder groups.

> *"So but so I ended up sending two of my CAR-T patients to the US to get CAR-T in March and April and May, June, that kind of area, because I was done with it, I'm like, I was I was not having it... I can't wait any longer. Right? And so we started getting we started, um, recruiting pressure from the Leukemia Lymphoma Society. We wanted some help. And when they put the pressure from there, back in May, they started approving for out of country?" (P1)*

Administrative Planning

The clinical and health system administrative communities worked together to assess the state of readiness and need for additional resources. This theme includes the challenges and facilitators encountered by these individuals throughout the assessment and planning phases as well as the development of the business case for the new program that was submitted to government in order to address the concerns. The following sub-themes were developed under this theme: inpatient capacity, allo-HCT, hospital and lab regulation, government decision making.

Inpatient Capacity

Administration and the clinical communities acknowledged the existing infrastructure and inpatient capacity would be a challenge for sites. The inpatient units where CAR T patients were to be cared for were reported to be operating at or near capacity, prior to CAR T and the pandemic. Coupled with the expectation that CAR T patients could stay in hospital for weeks after administration and would require 1:1 nursing for a substantial period and/or potential specialty support, clinicians and administrators agreed that a multicenter approach would be appropriate. Engaged and interested physicians at both sites also enabled this approach. Furthermore, at the Northern site, the HCT/hemato-oncology patient load already consumed roughly two thirds of the inpatient staffing and bed resources, so unit managers looked favourably on investigating a more-cost effective management strategy in this large population.

> *"You know, at the end of the day, the big hurdle to giving to implementing a car T-cell program in Alberta is clinical resources, just bed space and nursing to provide the care. And we didn't we don't have the capacity to do a whole bunch of extra admissions at the foothills. And so you know, I think it was fortuitous that Edmonton has decided to develop a car T-cell program so that all those patients don't fall on Calgary because we just don't have the capacity, right?" (P8)*

Business Case

A business case is a proposal created by a division of AHS to be reviewed by government for additional resources (new positions, equipment, training etc.), not including the cost of pharmaceuticals. It provides justification for undertaking a project and evaluates the benefit, cost and risk of alternative options.

The business case was a challenge to the adoption process for two reasons. First, it required cooperation in development from three different hospitals and a number of different services and units at each one. This diversity in stakeholders especially across different administrative

divisions was novel and time consuming and put significant strain on the clinicians leading its development.

Secondly, after funds were released, administrators in the CCA and at the site-level found that capturing costing information was difficult using this model as it required new accounting practices at the Southern site where CAR T was being provided under standard of care. In practice, departments tended to underreport the amount of resources used in caring for CAR T patients, leading to an under billing to the grant and government underestimating the future resource need.

> *"I can tell you we've had some trouble tracking the costs because the standard health care system is not used to submitting these things. So we're not getting billed for lab work that's being done. We're not getting billed for imaging that's being done as part of the program because a lot of people that are doing those things have not been involved in a trial like this before. So they don't they're not very good at submitting the costs. And so that's one of the things that is going to need to be discussed at the next meeting is we need better ways of tracking those things and making sure that people know how, how to submit those and that the costs do get attributed to the grant." (P6)*

Government Decision Making

Government decision making pertains to any of the processes that involved the ministry or discussions around additional funding. Initially engaging government was reported by participants as a difficult task for CCA leadership. However the innovation and cost-savings for the province aspects were interesting to government especially as they related to the ACIT001/EXC002 clinical trial:

> *"And I think there was almost enough of us around just every so often popping up that it finally got through to people's brains that the research and innovation piece in Alberta was something that government could go for, that they could get their heads around. And also, there was a potential cost savings,*

which was very attractive to the government at that time as well. Even the NDP government!" (P10)

The decision-making process government used to review the business case was perceived by study participants as long and unclear, particularly to those who had collaborated in the development of the business case. This created a feeling of uncertainty among clinicians trying to plan rollout of the program going forward.

"The process for approval was completely opaque. You know, once we submitted it to our higher ups, who then submitted it on our behalf to Alberta Health, that submission process is not clear cut. In other words, I was never clear as to who actually clicked send on the email, for example, there's no application portal or anything like that that made it very clear that your application had been sent. The review process is entirely opaque and took the better part of eight to nine months before we even heard that this was just going to get approved. And it was really only 10 months after that when we got a rubber stamp, and to this day, I actually don't even have an email that says you are approved. It literally was a notification by email from an AHS project manager saying that we're good to go and that there was going to be a press conference about 10 days after that I was given notice of it." (P14)

Clinicians felt there was a divide between AHS and government, which resulted in difficulty communicating upward the expected cost-savings of investing in CAR T.

"Now the business case is to secure clinical funding, which is the purview of Alberta Health, which is to provide the best quality of care, the best value for money, essentially. And given that we're considering expanding, there's into second line in lymphoma at least, um, this has a potentially, you know, multi-million dollar, if not billion dollar impact-- and that should be something that

the government is very interested in. But to my knowledge, there's no way that we could even communicate that information to them." (P14)

Higher-level clinicians and administrators echoed this sentiment, but in one case, felt that government may have finally started to listen due to their persistence and the magnitude of savings. Clinicians also reported that despite the clear pathway for communicating the benefits of CAR T upward, they were able to use a cost-savings argument to facilitate adoption in other ways, specifically through philanthropy.

After considerable pressure from below one physician recalled:

> *"You know, we still hadn't heard anything about the business case. So we had a meeting. I think [individual] was there and drafted a letter to go up, you know, go to the minister to say, you know, what's up with this? What's the holdup? And I understand from my conversation with the minister that he also had been receiving pressure from parents of children with ALL. And so at the announcement, he said, what did he say? He said, 'You know, I've been I've been hearing about these CAR T-cell things, you know, for, you know, from parents of sick children for a few months. And I spoke to my deputy and said, you know, can we get this thing going in Alberta? Can we do this? And the deputies said, well, that's what this is on your desk here. Sign that.' And so, you know, and then the funding started to flow. And then I think these pediatric parents had sort of grease the wheels along the way." (P2)*

Hospital and Lab Regulation

This subtheme describes the challenges and facilitators borne out of differential laboratory infrastructure at sites and the associated regulatory standards to which they adhere. At the Southern site, a well-established allogeneic transplant program with easily adaptable SOPs, physical infrastructure and a FACT-accredited cell therapy lab facilitated implementation of the commercial product. Novartis preferentially selected the ABMT as the initial Alberta site for these reasons. Although they have since relaxed their stance, allowing rollout at any site with a

'line of sight' to accreditation. Conversely, the Northern site operated within the sphere of the University of Alberta and was able to build a partnership with a suitable processing facility at that institution. As such, the laboratory infrastructure at both sites facilitated adoption but in different ways; the clinically focused FACT accredited laboratory at the Southern site brought interest from pharma, whereas the manufacturing facility in Edmonton enabled local production under more stringent (GMP) regulatory standards.

> *"I mean, I think Calgary was picked one hundred percent because they were already FACT accredited. So that is full stop what it was. We made a concerted effort to first go accredited again because we knew we had really high thresholds for lab audits and things. So it doesn't have anything to do with because I know some of our competitors don't need that need or ask for it. And again, we feel that we can relax that now that we're in major accredited sites, but our preference is still that they're FACT accredited." (P13)*

Clinical Trial Units

A clinical trial/research unit is the department of an academic hospital that employees nurses, managers and coordinators to conduct clinical trials funded by sponsors (pharmaceutical companies). At large enough centres with strong preclinical research traditions and funding, units may also sponsor clinical trials initiated by investigators (institutional clinicians). At the Northern site, because CAR T was offered under clinical trial, clinical research groups played a significant role in implementation. The CCI CTU perceived the clinical trial as too complex and novel to manage— initially opting not to support the IIT.

> *"But I think CAR T, I mean, I remembered actually talking to [CCI CTU manager], oh, ages ago, and she was like, 'Oh my God, we don't know what this is… and we can't get any answers and so on and so forth' like, OK, but I said, you wouldn't be on your own here. Like there's village of people trying to make this work, and I think they just put their hands up and said 'nope not for us'." (P10)*

The homogenized and independent IIT program at the Northern site was however reported by a previous staff member as a facilitator to the adoption process, relative to other centres without an IIT program or one specifically for certain tumor groups. Despite this administrative resistance, the academic community with assistance from disease foundations facilitated adoption at the Northern site by bridging the gap left by the CCI CTU and provided resources needed to launch the study. One of the reported challenges that were overcome through this collaboration were several provincial and federal regulatory approvals needed to provide the product under clinical trial.

Operational Readiness

Operational readiness encompasses the challenges and facilitators to the process of preparing sites to be able to administer CAR T and care for patients afterward once the additional resources were attained. At both sites, several key facilitators were captured: the institutional clinical experience from other interventions offered (auto-HCT, BiTEs, checkpoint inhibitors), and engaged nursing staff and educators.

> *"And part of that is because we were doing other clinical trials with similar type products that weren't CAR-T, and we had a lot of the SOPs and some of the experience in dealing with it. So we were doing these BiTe therapies, which are fairly similar and have some of the same side effects of CAR-T. And so the nursing staff, the physician staff, got used to dealing with these patients anyway and handling it, recognizing the toxicities early. So they said, well, we're comfortable with this now." (P6)*

Aside from these two facilitators, sites differed in the effect of other challenges. At the Southern site, a key finding was the clinical leaders felt compared to the effort required in acquiring the additional funding requested in the business case, preparing the site itself was less of a challenge. This was especially true at the Southern site, for which the 'nuts and bolts' of the program had been established prior to the business case.

The ABMT did, however, face a unique challenge to commercial products, a privacy impact by AHS, to ensure patients could not be identified by labelling of cell products throughout the chain of custody (covered by Federal regulation at the Northern site). A representative from the Southern site also mentioned control of funds through AHS related to OBP as a challenge to optimally utilizing the resources attained from the business case during operational readiness.

> *"So far, I wouldn't say that the resources, the funding isn't the issue. It's translating that funding into actual bodies. Our biggest problem right now that we're facing, which you've probably already heard about is the apheresis, you know, and we recognize this, we put it in the business plan-- they bought us a new apheresis machine. Right? That was part of the business plan-- and yet still we can't fit it in. Because we're still we are from a nursing and resource perspective, to deliver and proceed with apheresis, OBP has not allowed us to specifically designate areas for CAR-T… because our transplant program is over budget." (P2)*

The Northern site faced more operational readiness challenges due to the use of third party cell therapy laboratory infrastructure and provision of drug under trial, which were not issues for the Southern site. However, external change agents like FACT and other cell therapy programs helped to facilitate readiness by providing SOPs and guidance on the development of the new IEC program. Provision under trial also challenged operational readiness through delays caused by the creation of a new biosafety committee without a clear mandate or jurisdiction; these reviews, in turn, competed for time and energy with other tasks for which implementation leaders were responsible. Additional burden on inpatient nursing as a result of the increased requirements for monitoring patients on clinical trial was also a challenge. Prior to this IIT, clinical research was rarely conducted on inpatient units, a new system was developed to coordinate the clinical and inpatient units.

"In the more recent past, certainly in the last 30 years, there has not been a clinical trial on inpatients up until about one year prior to launching into CAR-T cells or deciding to do CAR-T cells. We had done the very first inpatient clinical trial, which was blinatumamab CD19-CD3 bispecific antibody with Roche that we had establish a lot of new protocols and infrastructure support around that as well." (P14)

Federal Regulatory Approvals

In this context, the federal approvals required to implement Made-in-Alberta CAR T were the No-objection letter from Health Canada, which clears the clinical trial to open for enrollment, and the addition of a 'novel substance' to the Domestic Substance List (Environment and Climate Change Canada), which allows its manufacture in Canada for clinical use. Both of these applications were completed by the study team constituting a novel venture for the CCI and Alberta:

"from a provincial level-- was the fact that there has not been a new therapy or substance produced out of Alberta for really decades from what I know, at least in the last 20 years let's put it that way. So as a result, we were doing something completely new from that perspective, number one, but number two, also because of the cell therapy that also had a viral manipulation. In Canada, there has only been one other trial CLIC-1901 that has onsite or decentralized production with production in Canada. Otherwise, all of the standard of care pharmaceutical products that are now approved had their manufacturing sites in the states and shipped back across, so there's no production in the country. So that led to a lot of additional questions, as well as a change while in the middle of preparing to do this, Health Canada had changed-- originally, they were doing the Environmental Impact Assessment as part of their application, but they outsourced that to Environment Canada. So we had to put a new substance notification application into Environment Canada, which was also new to anything in Alberta, but something that the CLIC-1901 team had to

deal with as well. So we were able to rely on their experience to navigate some of the potholes there. We were not entirely blemish free, but that was not surprising since how big the application was." (P14)

Elaborating on the environmental impact section of the application, the investigator of the trial reported:

"But I would I would argue that a lot of the application process and the hurdles that we had to cross with Environmental Impact Assessment is unnecessary… a lot of the questions were completely out of left field and completely irrelevant to a cell therapy. You know, for example, T cells are things that require very strict environment control, temperature, pH, you know, you name it, and realistically, for a T cell to spill on the floor means absolutely nothing because that CAR T-cell product would immediately die or at least very quickly thereafter, and there would be no impact to the local water system at all. But these are questions that we had to deal with and something that on an infrastructure level, on a national level, hopefully we can change in the near future." (P14)

<u>Delivery</u>

Delivery encompasses all participants' statements that speak to their experiences administering CAR T and caring for patients. During delivery at both sites, clinical staff reported the process as similar to transplant and had no difficulty in administering or caring for patients. Edmonton staff reported that provision under an IIT allowed for refinement of the process to better fit site needs.

Patient Experience (proxy)

Patients were happy to receive therapy closer to home as a result of the multicenter approach and felt the process went smoothly, remarking that it was easier to tolerate than an autologous HCT and similar to a bad flu. The unit manager from the Northern site and physicians offering the

treatment at the Southern site reported the delivery of CAR T and program launch were not challenging and went as expected.

Staffing & Human Resources

This theme captured participant views on the role of staffing and human resources throughout adoption. Participants remarked the main challenge to sustaining the program and in healthcare generally in the future would be retention of staff post-pandemic, due to burnout of frontline workers. Facilitators throughout the process were engaged clinical staff especially clinical nurse education at both sites. Unit and hospital managers also remarked that staff skills were improved through involvement in the care of CAR T patients and this would facilitate further growth of the program.

> *"It's too terrifying to even think. Yeah, honestly, it seems like there's going to be a mass exodus from health care, whether that be from burnout, different opportunities elsewhere. We're already seeing that, and I was actually listening to a podcast that was talking about pandemic flux syndrome and just the results of that and what that means for everybody was actually quite interesting." (P9)*

Future Considerations

During interviews, participants pointed out potential future challenges and facilitators to the sustainability and success of CAR T in Alberta which were contingent on how the field may evolve in the future. These were captured and grouped under the sub-themes of health system leadership, clinical development, indication expansion, scalability, spin-out/commercialization, small team, vein to vein time and outpatient delivery.

Regarding health system impacts, participants felt after implementation, leadership was more aware and engaged, potentially facilitating future growth and support of the program. Participants also felt this was important given the need to continue adapting the program to fit

the latest approaches, including outpatient delivery, which clinicians expected to reduce cost and change care pathways.

> *"The way CAR T's are delivered is going to change. There's a movement to do a lot of this as an outpatient rather than inpatient, which will change the cost involved and change some of the pathways too… it's going to change probably a lot less ICU costs and a lot less inpatient costs, patient monitoring, more need for you know, access to urgent assessments for patients after hours because they're not in the hospital. So I think it's important to track those because this it's clearly going to change."(P6)*

Industry perspectives reported scalability as a challenge, specifically for commercial manufacturers that rely on a single centre to manufacture products, but acknowledged that with more products coming to market the access to drug challenge caused by limited manufacturing capacity was being met. An industry perspective felt that the modality when provided in a decentralized model could provide significant opportunity for further development by investigators able to develop their own products to meet local need.

> *"…And I mean, that's one of the great things about having a tool and a trial at your institution that you can you can leverage, right? There are patients that are perfect fits for the commercial products, but there are a lot of patients that aren't right and there are patients that can't wait and having the ability to say, we can get a CAR to you in this time window and we know we can do it because we control every facet of it. We control the apheresis to the manufacture, to the infusion right. We know that this can be done in this window. It is an advantage." (P12)*

The majority of participants felt CAR T would continue to expand into other indications, soon supplanting HCT in second line NHL then in other cancers and autoimmune conditions.

"I think the data is already starting to trickle out there, so I think that in two or three years, the amount of autologous transplants will be going down and we'll just need to be able to provide this therapy to look Albertans in the eye and say, we're able to offer you the best therapy and the standard therapy at that time, which will not be autologous transplant, but will be CAR T-- at that point autologous transplant will be likely seen as substandard." (P1)

Regarding ACT-C01 in particular, one participant reported that they expected the future cost-savings to the province to be significant with commercialization and routine use of that technology, and added that the shorter vein-to-vein times associated with the product and the small research team could facilitate the cost-saving benefits conferred by commercialization and spin-out.

"What if you had the option to start with fresh material? Yeah, yeah. Right. And I mean, those are things that as an investigator, you, can you can create new trials that investigate those things and further drive development, right? Let's say instead of manufacturing for 14 days, you want to manufacture for seven days, right? Mm hmm. As an institution, you take on the development work and you see. Ok, perfect. Some things are the same, but some things are different. But is this safe? Yes or no? And then right, all of a sudden now you're talking about a fresh product that's manufactured in seven days." (P12)

"Yeah, that's what I think, you know, and it all really depends on how this Made-in-Alberta thing goes, right? I think that's going to be a game changer for us if the Made-in-Alberta product is actually proven to be an effective alternative and that we can produce CAR-T locally." (P2)

Of note, the ‘Stakeholder Diversity’ theme in the initial section captured quotes that described a larger and more diverse group as a challenge, supporting the idea that there may be correlation between group size and efficiency of adoption and implementation processes, as small team size was reported as a facilitator here.

> *“So that smaller team that you guys had really, I think, allowed everybody to have a great and deep understanding so they really can see the importance, right? Hey, it's a cell count, but it actually translates into this right and this is what we're ultimately going for...” (P12)*

Conclusion

Stakeholders faced challenges and found facilitators to the adoption and implementation of CAR T in Alberta throughout the adoption process. To capture these, interview data was coded and quotes were organized into sub-themes and then themes and finally grouped by whether they were site-related or -unrelated as a preliminary analysis of the factors at play during the process which was presented above. The next step in the analysis of these results was to assign each challenge and facilitator to a construct within the consolidated framework for implementation framework to present them in a more standardized way and to evaluate its suitability in characterising the challenges to and facilitators of implementing complex pharmaceutical interventions.

Deductive Analysis

Following inductive coding, challenge/facilitators were assigned to one or more constructs under one of the five CFIR domains: Innovation Characteristics, Outer Setting, Inner Setting, Characteristics of Individuals, and Implementation Process. This approach was chosen to present results in a more intuitive and standardized format, which also allows different stakeholder groups to quickly see where they fit in the process enabling them to quickly draw conclusions for future innovations. A full list of CFIR constructs within each domain can be found in Table 1. Results are presented in the order found in the official CFIR codebook.

Evaluation of the Suitability of the CFIR

The key ideas and C/F identified during inductive coding mapped well onto the CFIR constructs, with several exceptions. In these cases, key ideas and C/F were assigned to the constructs of best fit and presented with qualifiers. The difficulty in mapping emerged from the differences between CAR T and the types of interventions usually assessed with the CFIR.

Because CAR T was a commercially available product, issues around ownership, legality, and access and availability to the innovation are relevant. Key ideas, and C/F on this topic were mapped to the external change agents, perception of source, or relative advantage. For researchers studying the implementation of marketed products, especially those which are expensive and controlled by a large company, a new construct of this nature under innovation characteristics could be created. This construct would be less relevant to the assessment of implementing lower cost/risk products and/or publically available interventions.

The investigational CAR T product actually changed during adoption, (dosing, and manufacturing method changes) and was evaluated during implementation and key ideas and C/F emerged as a result of its dynamic nature. These quotes were assigned to either the adaptability or reflecting & evaluating constructs. Delineation of results may be improved in the future with the inclusion of a novel construct in the innovation characteristics domain related to technological malleability (i.e. how the innovation itself changes during the process).

The CFIR does not have a construct for external factors, only external change agents. Although these were considered as synonymous in this study, future separation would improve clarity of analysis by including a construct/domain to address external factors (i.e. natural disasters). Statements are made by participants that related to decision making and risk management were observed. These fit well to the Inner Setting constructs of Networks & Communications, or Process constructs Planning and Executing, but I suggest the addition of a Process construct between these two referring specifically to statements about the decision making process.

Lastly, two novel constructs were also created to further differentiate constructs and improve clarity (i.e. 'Hospital' and 'Manufacturing Infrastructure' under the 'Structural Characteristics'). It is worthy of note that more of these early stage C/F than expected fit well into the CFIR, suggesting a potential role for this framework in describing C/F unique to CTPs in phase I or II clinical trials.

Consolidated Framework for Implementation Research

I. Innovation Characteristics

Evidence Strength & Quality

Clinical trial data empowered physicians driving adoption, especially those developing an investigational CAR T product:

> *"… Had we been trying to do something that [didn't] already [have] an established track record of any sort that would have quite a bit more difficult. Again, I think part of the motivation and the reason why we were able to break down some challenges is because CD19 directed CAR T-cell therapy was wildly successful."(P14)*

The evidence of efficacy enabled champions to pressure government to expedite reviews and approve clinical funding:

> *"I told them that there were people dying. I kept it simple. There were people dying. There was a new treatment that would work, but it would be a half million US for every patient. We had to buy it and we could do it for fifty thousand dollars, at the Cross per patient. But they had to help. We had to push from above." (P3)*

Relative Advantage

The relative advantage construct in this context refers to the perceived differential clinical benefit between the standard of care and each technology, as well as any incremental advantage between the two technologies themselves. The technology at the Edmonton site offered a relative advantage over that of the southern site due to the benefits conferred by a locally managed point-of-care manufacturing process:

> *"So there were certainly the cost perspective, so it should be cheaper to do the made-in-Alberta thing. There's also the not relying on commercial entities who could pull the rug out from under you at any time. There is the not relying on things having to be frozen and go back and forth to treat people who are really very sick."(P10)*

According to a physician at the southern site, bridging patients to CAR T is their primary clinical challenge:

> *"I'm happy now. Very happy now because we can get it. That isn't the issue now. It's more the um, the patients themselves... trying to get fit patients, getting them before they get too sick for CAR T. So that's really the big issue, but, uh, we can fit them in if they're eligible for CAR T." (P2)*

> *"And then then we have a list of people who were referred, but some issue happens. They weren't either eligible from a patient perspective, so you can see the numbers are about the same. So you had a lot of patients who referred who didn't end up getting CAR-T. One patient, we actually manufactured a product, but he died before we could infuse, he was too sick. This patient was too sick to get CAR-T at the beginning, so she never even underwent apheresis…" (P2)*

> *"The information I got speaking with Kite today-- like time between enrollment and infusion was forty one days, which actually fits with the rest of Canada, so I think we're doing OK in terms of our time." (P2)*

An industry voice re-iterated the importance of turnaround time, adding it could be worth excess toxicity to minimize disease progression during manufacturing:

> *"...right now, the data that's available, it is kind of a, I guess, a dealer's choice, right? There are slot availabilities, there are known toxicities, which one fits what my patient needs, what the patients in my community need, right? Mm hmm. You know, as an example, if you are not able to get products or we'll use an extreme example 40 days, right? And a majority of your practice is aggressive, large cell lymphoma, that's a long time. Right? So how are you going to manage those patients, right? What options are available that are better suited? And would you choose a product that has a little bit worse of a toxicity profile if it gets to these patients faster?"*

Adaptability

Delivery of CAR T is similar to, but less complicated than HSCT from which patient identification, screening, administration and monitoring processes can be relatively easily adapted especially with FACT guidance:

> *"Because again, we've done the autologous and we've done kind of that process for a very long time. They're comfortable with the actual infusion process, and I don't think that was too much of a departure from standard of care that we do with the autologous patients." (P9)*

> *"Also with just our equipment and the process of doing the actual CAR-T infusion where we were able to align it very similarly to the stem cell transplant protocol. So then when we're doing the instruction with the nurses, it's not as complicated as if it would have been mandated from a commercial product, right? It might have been quite different and a lot more difficult to do the education part." (P7)*

At both sites, previous experience with BiTE therapies made for a good starting point around staff education on the recognition of immune-related side effects:

> *"And part of that is because we were doing other clinical trials with similar type products that weren't CAR-T, and we had a lot of the SOPs and some of the experience in dealing with it. So we were doing these BiTE therapies, which are fairly similar and have some of the same side effects of CAR-T. And so the nursing staff, the physician staff, got used to dealing with these patients anyway and handling it, recognizing the toxicities early. So they said, well, we're comfortable with this now." (P14)*

The southern site was subjected to audits and reviews mandated by the company, which are unique for each CAR T product:

> *"So that's the problem with the clinical trials and commercial product... if it's not the same company, you have to do the exact same thing. So like with Kymriah and Yescarta, we had to do everything separate-- so the teaching, even though it's the exact same CRS, it's the exact same neurotoxicity, it had to be separate so we got the double dose of everything." (P2)*

Trialability

Trialability is defined as: the ability to test the innovation on a small scale in the organization, and to be able to reverse course if warranted. As a whole, the implementation of either technology could not be trialed due to its scale and cost. However, the trialability of different elements (dry runs for apheresis and administration) during implementation at the CCI was employed prior to enrollment in trial and staff felt it useful:

> *"...so I think if it was a commercial product, it would have been very standardized and probably a bit more rigid. I think by having it, as investigator-initiated trial, we're able to use our real life clinical skills and then we're able to do amendments*

and adjust the protocol. So it is more applicable to how the Cross Cancer Institute runs essentially."(P7)

Complexity

The complexity of implementation is the perceived difficulty of the innovation, reflected by duration, scope, radicalness, disruptiveness, centrality, and intricacy and number of steps required to implement. Compared to the implementation of the commercial product, the IIT was perceived as being far more complex and prone to exposing the institution to risk. The group most responsible for attending to this complexity was the clinical trials unit of the CCI, who declined to sponsor the trial. One of the administrators at CCA recalled:

"...I think CAR T, I mean, I remembered actually talking to [CTU manager], oh, ages ago, and she was like, "Oh my God, we don't know what this is, and we can't get any answers and so on and so forth" like, OK, but I said, you wouldn't be on your own here. Like there's village of people trying to make this work, and I think they just put their hands up and said "nope not for us". (P10)

Another participant elaborated by adding that the CCI CTU had never really sponsored a clinical trial, because none of their research had ever actually made it to the clinic before:

"Part of the concern was whether or not the Cross has the personnel and HR to be able to handle some of that sponsorship responsibility and the fact that they'd never done so up to this point. So as a result, due in part to a lack of familiarity and lack of confidence similar to that of the inpatient delivery, we then had to turn to the U of A as the alternative." (P14)

The COVID-19 pandemic, which occurred during the implementation of CAR T, added complexity to adoption by forcing the Edmonton site to move the delivery site to a different institution.

"That's when COVID really kind of ran amok with things, and we were asked to no longer provide care at the U of A hospital because of resource allocation and scarcity from COVID patients. We used that as an impetus to be able to bring the treatment to the Cross and we were fortunate to have been able to do that ever since" (P14)

Cost

Cost of apheresis resources played a small role in adoption. At the Calgary site, the apheresis service falls under nephrology as opposed to the CCI which manages that service itself:

"So we're big users of their service. But the nuts and bolts is done by nephrology" (P8)

Regarding additional costs:

"…the other thing was apheresis and just inpatient resources in general across, you know, in haematology, but across the foothill site, the yeah, because the complication rate was high for sure." (P8)

"So if we're looking at the apheresis piece of things, you know, it's similar to standard of care. Obviously, it's a shorter procedure. We can guarantee that it's going to be usually a one-day collection. So that's pretty standard. Where we're getting into some additional costs for us right now would be with the inpatient stay because we are having that one to one nurse for the first 48 hours just because we were wanting to watch them. So I don't know if that's something that we're going to continue moving forward. And I guess that's a larger discussion to be had, but that's kind of where we're at with the additional costs right now. Otherwise, there's no real extra." (P9)

Speaking about their experience developing the business plan to fund the program, a clinical expert in Edmonton stated:

"So for the business case, our experience was: we outlined our needs for a clinical program and it went to a project manager hired by Cancer Care Alberta. And after our clinical needs were delivered, there was negotiation to whittle down the need for the program and the establishment of it to the bare minimum. And even then, we got even less. So this is a classic case of what happens in government of, 'you know what it takes to devise a successful program but we will not give it to you'… really where the difference between public health care and a private entity like a company would look at this differently." (P1)

Managers in Calgary echoed the sentiment but to a lesser extent:

"The previous bone marrow transplant director used those relationships very well and actually presented himself nicely to the AHS board as well for this plan and was chosen to really represent all the hematologists within Alberta to present the Calgary model of the CAR-T program, which did involve some involvement from us. But it didn't necessarily allow for a full translation of all of our wants and needs to get our program up and going." (P8)

Because the northern site was able to secure access to drug at no cost to government under clinical trial, hospital leadership felt that government finally began to see how beneficial local clinical research can be for their budget:

"And I think it's also highlighted the value of doing these clinical trials because if I'm government now saying, well, this is what it's going to cost the standard of care. But if we support Edmonton and Calgary in opening this through a clinical trial, we don't pay for the product. We can do all the other stuff with. That product itself costs $300-$400000, so there's a significant saving to the system where that money could be redeployed. And I think that's probably been an eye opener for people in government. We've been trying to tell that from just standard drug savings for years and finally they're started to listen. But this, I think they got the message loud and

clear is $400000 drugs that if we do it through a trial, we get for nothing. We just need to put all these other things in place that we would have been doing anyway, giving the standard of care drug. So I think it's highlighted to lots of people who really didn't haven't seen that the value of doing a lot of these things through trials in terms of the cost saving, but also we're moving things forward." (P6)

"So I think personally that when the cost came back for those first few patients from the US, then that's why they approved the funding in August. Ok, because it costs like a million plus to do everything, right?" (P2)

Perception of Source

The clinical trial unit responsible for conducting the study at the Edmonton site was reticent to support the project due to the perceived source and risks. According to the principal investigator:

"I think there was quite a bit of fear about CAR T cell therapy. Yeah. And people had heard about catastrophic cytokine storms. People had heard about the need for ICU and so on and so forth. And I don't know whether they just said we can't handle that if people have to go to ICU they need to be in the university hospital. I don't know. And then of course, we had biosafety at CCI going well I don't do anything with clinical trials for this either, so I can't provide any oversight. And even though [hospital director] was such a champion, I don't know what happened with clinical trials and why the why the CTU didn't take this on." (P5)

At the Edmonton site, the study team went through an ad hoc biosafety review process; something to which other commercial CAR T products (including Kymriah) and previously implemented gene-modified therapies had not been subjected:

"...because it is a cell therapy that is manipulated using a viral vector and in our case a lentivirus, we were asked about the safety of it all. There was a discussion from years ago about establishing a biosafety committee to review clinical trials

and research in general within Alberta health services, but never have really gained traction. Because of our push unfortunately, we had to help set that up. So essentially, Alberta Health Services became quite nervous about giving a product that was virally manipulated, and so they finally decided to use this as the impetus to try to get a biosafety committee together."(P14)

The managers of the hospital units were engaged and showed unprecedented excitement during the implementation process:

"I know that [person] had initially taken [person] and I aside and said that this is something that he was looking at doing. And, you know, from that onset, we were very supportive of him and this initiative because it's exciting and to be able to bring that to Edmonton and to the cross and to have somebody as talented as Mike running this trial, I think that was an exciting opportunity." (P9)

Finally, anxiety among frontline physicians, nurses and other clinical staff experiencing difficulty referring patients was increasing:

"…so I ended up sending two of my CAR-T patients to the US to get CAR-T in March and April and May, June, that kind of area, because I was done with it, I'm like, I was I was not having it… I can't wait any longer."(P2)

II. Outer Setting

Awareness and Prioritization of Patient Needs & Resources

An individual in a strategic leadership role at CCA was responsible for gathering operational information to acquire additional funding for both sites:

"…it was looking at what are the services that we plan to offer. What's the patient need in going through? What are the I think the clinical side of it in terms of the indications and all of that need to be put in there, the rationale for why we should

do it in Alberta, all those things needed to be collated into a package that we could bring on to both AHS leadership and Alberta Health. So that was pretty much [individual] focus throughout that first year." (P5)

Aside from CCA, AHS was only reported to be involved the adoption process at two points. The Contracting, procurement and supply management department was involved in the legal processes of purchasing Kymriah, and was reported by an industry representative as efficient and hard-working:

"And honestly, the team at AHS, they were they were working through Christmas on this just like I was. So our global teams were as well, and the reason we did that was because they had patients they wanted to line up for January. And so it was a pretty big deal to have that all set to go because again, it's, you know, you can't do some of the other things till that stuff happens" (P13)

The other point in the process was the approval of the business case by the CEO of AHS which is covered in the inner setting and process domains.

Cosmopolitanism

Cosmopolitanism is the degree to which an organization is networked with other external organizations. AHS networks with other provinces during the practice of sending provinces out-of-province to receive treatment. Physicians had difficulty in securing availability in other Canadian centers. This was due to the fact that there was no reciprocal funding agreement in place to cover hospital expenses until August 2020 and also limited capacity at the few institutions providing CAR T (a phenomenon exacerbated by the pandemic). These challenges affected clinicians at both sites:

"So it was provincial funding. So Alberta would have had to reimburse Ontario for any of the costs that's including the product, but also clinical care. So the inpatient nurse, inpatient time, nursing time, any of the additional medications, investigations and tocilizumab if needed." (P14)

"Interviewer: Did you try to send them to Montreal or…"

"Well, they don't have the space! You think there's like one centre in Quebec and one centre in Ontario that was open, PMH had just opened in April of that year. There's no way they would be able to serve out of province, right? They just can't, they just don't have, they're like, they're barely keeping up... Now they can, so the PMH is doing, they have a whole CAR T service. They're doing like four or five CAR-T patients a week. Wow, right? We don't have that, but they have the structure for that, which is fantastic for them. So they're doing a lot of out of province, they're doing all of Saskatchewan, many B.C. patients are going there instead."(P2)

The industry approach to rolling out CAR T was to move from more to less experienced sites sequentially, allowing for passive diffusion of knowledge across institutions which was found to be useful by a clinical stakeholder:

"…there were a couple of webinars with Sick Kids and PMH, and so I think we found those kind of useful, you know, in terms of, did anybody help us do the nuts and bolts of the SOPs? No. But, you know, the SOPs sort of flow from FACT guidelines and how your program is structured." (P8)

"If you have a surgeon that's really good and is completely trained with your product, you're going to go there first and make sure that it's successful and make sure that you can work out the kinks. And so that was our strategy was work out the kinks of process because we if you do it well, then they can help teach some of the other sites. And so that's what we were trying to do was foster some mentoring between some of the other sites. So say Toronto SickKids as sites here we say here's a person versus it just being Novartis. We want them to talk to another clinical site and learn what some of their [clinical and operational] hurdles [were that] they had to overcome. And so that's what's been really successful" (P13)

Peer Pressure

This construct refers to the mimetic or competitive pressure to implement an innovation, typically because most or other key peer or competing organizations have already implemented or are in a bid for a competitive edge. Evidence of the desire to implement as a result of peer pressure is found primarily in the reports of providers during the initial phase of implementation, however these sentiments are more fiduciary than mimetic in nature. As such, they are considered in the Championship section.

III. Inner Setting

Inner setting of the CFIR constitutes the sites of adoption and the individuals promoting adoption there. It considers the structural characteristics (age, maturity, infrastructure etc.), social factors (communication networks, culture) and state of the readiness (access to knowledge, available resources) affecting the process 'on the ground'.

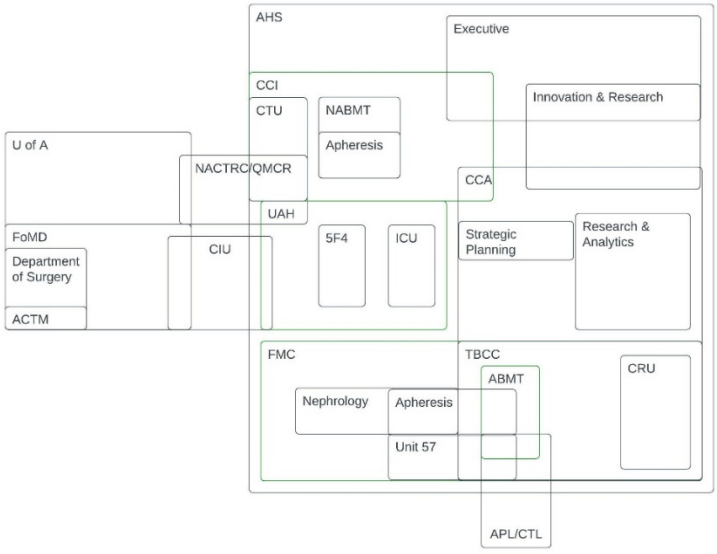


Figure 9. Inner Setting: Hospitals, Administration and Health System Administration. Acronyms: U of A: University of Alberta, FoMD: Faculty of Medicine and Dentistry, ACTM: Alberta Cell Therapy Manufacturing, CIU: Clinical Investigation Unit, NACTRC: Northern Alberta Clinical Trials Centre, AHS: Alberta Health Services, UAH: University of Alberta Hospital, QMCR: Quality Management in Clinical Research, FMC: Foothills Medical Centre, CTU: Clinical Trials Unit, CCA: Cancer Care Alberta, ICU: Intensive Care Unit,

TBCC: Tom Baker Cancer Centre, ABMT: Alberta Bone Marrow Transplant Program, CRU: Clinical Research Unit, APL/CTL: Alberta Precision Labs/Cell Therapy Laboratory, NABMT: Northern Alberta Bone Marrow Transplant Program

Structural Characteristics

Hospital Infrastructure

Throughout the adoption process, the age and physical infrastructure constraints of the Cross Cancer Institute and Foothills Medical Centre were repeatedly expressed and exacerbated by COVID:

> *"…the Cross Cancer itself and Foothills…are old buildings-- you know, the Cross is 50 years old and therefore the infrastructure is built off of what their projection of the population would have been back in 1980, 1990. So we're certainly outstripping our resources right now just because we've met that capacity and then exceeded it from what we can handle both on outpatients and inpatients… I think COVID, has also really highlighted that as well, just because of the need for resource allocation during a pandemic or any type of crisis situation." (P14)*

Here the medical director of the facility in Edmonton elaborates:

> *"Yeah. So the money is one thing, but having the actual physical infrastructure to do it, the chairs in apheresis, the staff to do the apheresis, the inpatient beds… if you start increasing those numbers at some point you just don't have the beds because all your other stuff, you still have to do. Yeah, we're seeing it with COVID, it's taking up all the beds. So we have to stop doing a whole bunch of other things because we just can't do them because we don't have the beds to do them."(P6)*

The clinical director of ABMT reported the same major challenge:

> *"You know, at the end of the day, the big hurdle to implementing a CAR T-cell program in Alberta is clinical resources, just bed space and nursing to provide the*

care, and we didn't we don't have the capacity to do a whole bunch of extra admissions at the Foothills." (P8)

The director of BMT remarked that they were glad Edmonton had simultaneously decided to pursue a CAR T program as it reduced their infrastructure burden:

"...I think it was fortuitous that Edmonton has decided to develop a CAR T-cell program so that all those patients don't fall on Calgary because we just don't have the capacity." (P8)

The impact of a lack financial resources constraints is described in greater detail in the 'Available Resources' section of the 'Readiness for Implementation' construct.

Health System Administration

One of the participants leading clinical research at the Northern site reported:

"...there will never be a process that is friendly to innovation because we are in bureaucracies that are counter-innovative. They actively oppose innovation-- not by-- they're not bad people. It's just by virtue of a big company-- a big publicly funded company will be gridlocked, it will be bureaucratic. That is the natural state. Ok it's an unnatural thing to actually get the kind of changes in place that leads to some successes like this. And you just can't change that." (P3)

The funding structures that go along with the complex organizational structures create a soiling effect that makes collaboration between departments or hospitals difficult. If collaboration is needed, as it was in the extremely stakeholder-diverse process of CAR T adoption, the process becomes convoluted, involving an ever-growing number of middle managers without any clear authority to proceed from above:

"So that is one of the challenges in getting innovation into AHS. If you have to work across different areas within the organization because there are different decision

making structures, not necessarily the best of relationships all the time, and the big thing is budgetary constraints because everybody's budget is in their—'this is mine. This is mine. This is mine'." (P10)

One participant also compared the funding and organizational structure of the sites, describing Calgary's program in favorable terms as the result of a decision made 30 years ago:

"So they used the relationship between the Foothills Hospital and Tom Baker, which is the cancer care hospital down in Calgary. The fact that they're adjacent together means that, they can, Dr. Russell, in the past had really built himself a nice program with both the inpatient portion and outpatient process as well, or program as well from the foothills and the Tom Baker, respectively. He did a masterstroke really in creating the program the way he did, because there's a lot more flexibility, if it's unable to be offered in one there's a potential of it being offered in the other." (P1)

Networks & Communications

Biosafety review generated deadlock[ix] that proved to be a time-consuming element of the implementation process. NACTRC acting on behalf of AHS and the University was essentially captive to the biosafety committee and couldn't authorize the study without approval from above:

"We have a bit of a role, but not really. So again, no clear pathway. Who was going to sign off on it from an AHS perspective? So that was a lot of conversation. And then of course, we had the NACTRC involvement there. So the lawyer from NACTRC, who was pretty sure she understood the legislation and the regulations from a legal perspective, but she didn't really get it from a from a biosafety perspective. And then I think relations broke down somewhat there. So [person] and I, I think, did some work on helping to try to repair relations, but then also

[ix] A deadlock is a situation in which no member of some group of entities can proceed because each waits for another member, including itself, to take action.

trying to figure out, well, repairing relations is fine, but how on earth are we going to get biosafety sign-off from AHS?" (P10)

Identifying the individuals willing and able to authorize or sign-off on things was raised as an issue by clinicians:

"It's really hard to find the right person to stick their head out of the water and say, I'm the right person here, and I'm going to sign off on this. Be sure that people who are in those positions have the ability to do what it takes to do their jobs, which is to regulate and look at and view these programs, if there's a clinical need that can be highlighted to AHS-- with the example of the biosafety officer."(P1)

Culture

According to the former director one site's clinical trial unit, as an innovator you should expect to face resistance from AHS. The culture of AHS, as defined by its norms, values, and basic assumptions is one of indolence and obstinacy:

"You're going to have to ruffle feathers, OK? Because the natural state is these people want to show up at nine, leave at three thirty and not do anything different than they did yesterday."

"I mean, that's just-- the vast majority of AHS employees are like that. Maybe the upper administration wants some innovation, or at least will use the word. Some of them actually might be creative, innovative people. But very few people have actually ever done anything innovative, and they're often the ones that are on their innovation committee have never actually done anything and shouldn't be there." (P3)

This culture is also site-independent and thrives in places farthest from the frontline of care, like the clinical trial/research units:

"...we are fed up with waiting for the CRU because that was the biggest delay -- the contract issue because we can't do anything unless you have a contract, you can't even see the protocol without a contract reviewed and signed. And then after that say, I want to do this trial review the protocol, I've reviewed it with all my mates and said, ok we're all onboard. We want this trial here. I then have to apply to this trial committee and they have the word rapid in it-- Rapid trial review and there's nothing rapid about it. It's like there's nothing rapid about it... And you have to go through this process like you're on the list to go to this meeting and it takes three months to get to that meeting…" (P2)

When comparing the sites themselves and the organization of physicians, one participant remarked that regarding clinical trials, the culture was more collegial in Edmonton:

"I think they're all kind of looking at it as a zero-sum game, and there might be a bit more in-fighting down there, whereas here we try to, I think, work more as tumor groups together and your friends and colleagues, you do my trial, I do your trial. We all are better off when you collaborate and I think it's a bit more socialistic or democratic or something up here than it is down in Calgary, where they're a bit more individualistic and entrepreneurial. I think it's just a different culture." (P3)

Implementation Climate

Laboratory-modified cell therapy was something new for the Northern site, which brings institutional challenges-- according to a representative of the bio-manufacturing industry:

"You need the regulatory support from your institution. You need the environmental and health and safety support. You need the GMP manufacturing team support. You need the QA/QC team support to do all of those things. And I think specifically for you guys, it was really the first big undertaking where an investigator at your institution went through that entire process, right? And every institute will be different. But there are parallels in the fact that every group needs

a lot of other teams support, right? You generally can't just do all of these things themselves.

Now, some institutes have been doing and running trials like this for the better part of 20 or 30 years. And so for them, some of these things are a little bit old hat, right? But there still is a lot of work behind the scenes that has to be done and making sure that all of the preclinical data and the clinical submission package is ready to go."(P12)

Despite a culture of stagnancy, champions in the clinical and administrative sphere persist:

"Expect that anything innovative is going to be an uphill struggle and because you're leading, you're going to know you're leading because every day when you go home, look in the mirror, you've got a bunch of arrows in your back."(P3)

They face a climate of resistance to change, especially if resources are required from other portions of the organization:

"Cancer Care Alberta said this is important, it's important for cancer treatment, it's important for people, then you've got other parts of AHS coming back and saying, Well, that's great Cancer Care, but this impinges on our budget, so it impinges on our ICU budget, it impinges on our-- where we provide apheresis, it impinges on that. How are you going to be sure that we are not going to end up having a hole in our budget because you want to do this novel treatment that involves centers outside of your tertiary cancer treatment centers?" (P10)

Tension for Change

Tension was greatest for physicians:

"Yeah, so definitely partially motivated through a lack of access, seeing some of my own patients suffer from not being able to go ahead and get CAR T cell therapy,

especially since I've been doing it just a few years earlier on a clinical trial at [Clinical Institution]. So that was definitely the motivation, one of the bigger motivations, I should say." (P14)

"...I was done with it, I'm like, I was not having it... I can't wait any longer. Right? And so we started getting we started, um, recruiting pressure from the Leukemia Lymphoma Society. We wanted some help. And when they put the pressure from there, back in May, they started approving for out of country? (P8)

For unit managers the cost of treating hematology patients in hospital and managing them post auto-HSCT is the major contributor to costs for the inpatient department, so implementing CAR T could become significantly cost-saving in the long run:

"I was just working on our bed stats yesterday, and it is about probably anywhere from 65 to 75 percent of our bed base right now is haematology or stem cell transplant patients, and so if we're able to adapt some of those treatment regimens or change the trajectory of their stem cell transplant and kind of move away from that inpatient perspective for some additional patients, obviously that's going to have a positive impact on patients and our budget." (P9)

Relative Priority

As referenced previously, due to the tremendous tension for change from providers the relative priority of implementing CAR T was expressed to saturation, especially for the IIT in Edmonton:

"...so I stuck my neck out a lot for [person]. So basically, we socialized the idea this is the most important clinical trial that we could be doing. I mean, I'm on the record as saying that at departmental meetings both the Department of Medicine but also Department of Oncology that nothing else mattered in the clinical trial unit but getting the CAR T program off the ground." (P3)

Organizational Incentives & Rewards

There were no organizational incentives or rewards described during interviews or found during the documentation analysis during the construction of the timeline (Chapter 1). As reported in the interviews, opportunities to reward or incentivize individuals for their hard work went unused actually having the opposite effect in the case of the funding announcement:

> *"And I told him myself, you know, I told him that he needs to put the humble thing aside and for the sake of the program, start bragging because it's not bragging. It's real. And it just gobsmacked me with the CAR T announcement. It happened down in Calgary when, as far as I could tell, most of the innovation actually came from Edmonton. But there it is." (P3)*

> *"It literally was a notification by email from an AHS project manager saying that we're good to go and that there was going to be a press conference about 10 days after that I was given notice of it. And to that point, that press conference was actually in Calgary, and I actually wasn't even invited until the day before to participate in it. Not that I really needed to do so, but just recognition of effort was what I was looking for there. And so to have that flash in my face as a Calgary initiative was a little bit odd..."(P14)*

Learning Climate

Clinical staff had the training materials developed by a knowledgeable and experienced individual, who took a provincially harmonized approach to teaching staff:

> *"I think with my curious little brain going and talking to [individual] about this and hearing whispers of it, you know, its coming, its coming, its coming. I thought, Well, OK, what can I do to support it? And I think I actually was the one that said, I'll take it. I'm interested. This is cool. This is going to be ground-breaking. So I think it was part of my persistence in, you know, talking to my manager and saying like, I really want to be a part of this, like, can we do something with this?"(P4)*

The CNE then proceeded to information gather with other sites and assessed the needs for knowledge generation and translation:

> *"Everything and anything, basically, we had to, you know, find out who our players are, build our, you know, our experts, reach out and build bridges with our Calgary partners, not just within CCA, but outside of CCA. So Unit 57 at the Foothills, who was not familiar with how as a provincial group we operate where we reach out and work together to come up with things."(P4)*

> *"We could find that also out in in journal articles and through other experts, but we wanted to invite them to the table as well to be a part of it and to, you know, because they brought such some, some experience that we didn't have. We also reached out to Alberta Children's and the Stollery as well to try and get them involved. And, you know, because we're all in this together and replication and duplication within education is not ... there's a lot of work and resources that are put to recreating the same thing. And so, you know, we're getting the groups together, getting the managers on board to support this and then having some really good conversations and, you know, being listening to each other and building that rapport was a big part. But the other part was also reaching out to our experts."(P4)*

Evidence of success can be found in the fact that the knowledge translation group continues to meet and attract new members:

> *"...the initial working group people, plus a few more, have come back to actually start to redevelop the annual education requirements or looking at how we can give an update that's harmonized again? And I'm quite pleased at the enthusiasm as we have probably 10 people on that working group from all different provincial backgrounds so which, you know, wouldn't have happened before. But CAR T has built that bond with us, so that's a good thing."(P4)*

The harmonized approach has also allowed for the utilization of these teaching materials across the AHS organization through a digital platform for information sharing:

> *"So I thought that by having, you know, by taking a harmonised approach, sharing the knowledge and getting it into a space that is not hid on someone's SharePoint site away from everyone else, it should be accessible to anyone within AHS you know, whether they be in emergency or in, you know, critical care. They still had access to learn about CAR T and see what where the future with lies with cancer treatment. And you know how exciting this could be." (P4)*

Readiness for Implementation

Physician interest, the expectation of CAR T becoming SOC, and a large unmet need led to the decision to implement on a broad scale. As reported by one of the facility medical directors:

> *"The decision to do it at both [sites] is because there's interest. It's going to be standard of care, in both places. And again, the amount of resources that goes into a program like this now, particularly to start-- it would be too much for one center to be able to do."(P6)*

The differential infrastructure at each site posed a challenge to simultaneous bicentric implementation and the lack of FACT accreditation in Edmonton at the time represented a major challenge and facilitated the development of a locally manufactured alternative product:

> *"[Individual] was very keen at that point to start a trial. You know, my impression at the time was that, you know, he was doing that so that, Edmonton would be able to give CAR T cells because it was clear at that point that programs needed to be FACT-accredited to give commercial product. And you know, at that time, there was no commitment on behalf of anybody, either at cancer care or at the cross to develop a fact accredited BMT program in Edmonton. So my impression was that*

the primary impetus for the clinical trial was to kind of get a foot in the door for Edmonton."(P8)

How the CCA balanced these considerations and came to choose the bicentric approach is described below as reported by the director of planning:

"...So with Calgary and Edmonton, as you say, being in different places of readiness, the business case needs to talk through that. So if we were going with just one place, what would be the reason for that? When would we expand? How would we expand? So answering those questions along the way, I think, are important in the case as well, and if there's a good reason for it to only be in one place. And often that is the case if it's something really specialized because we're looking at, how do we provide that safe quality care that's still operationally feasible, sustainable and some of that gets down to minimal competencies and volumes of patients, that sort of thing. There's a certain amount of fixed cost infrastructure that's required. The more you spread out as well. And so trying to balance those off in a fiscally responsible way. So in the case for the CAR T seem to be a case to spread it out across the province, but also looking at where people were at, what kind of timeframes would it take to get everybody up to whole?"(P5)

1. Leadership Engagement

Leaders were engaged in the implementation process:

"...so I stuck my neck out a lot for him. So basically, we socialized the idea is this is the most important clinical trial that we could be doing. I mean, I'm on the record as saying that at departmental meetings both the Department of Medicine but also Department of Oncology that nothing else mattered in the clinical trial unit but getting the CAR T program off the ground." (P3)

Lower level hospital managers were even more engaged and excited to participate in the implementation process:

> *"I know that [individual] had initially taken [person] and I aside and said that this is something that he was looking at doing. And, you know, from that onset, we were very supportive of him and this initiative because it's exciting and to be able to bring that to Edmonton and to the cross and to have somebody as talented as Mike running this trial, I think that was an exciting opportunity." (P9)*

2. Available Resources

At the CCI most of the inpatient resources are consumed by patients with hematological malignancies that are now being treated in clinical trials with future iterations of CAR T, further underscoring the need for implementation and investment in future R&D:

> *"I was just working on our bed stats yesterday, and it is about probably anywhere from 65 to 75 percent of our bed base right now is haematology or stem cell transplant patients, and so if we're able to adapt some of those treatment regimens or change the trajectory of their stem cell transplant and kind of move away from that inpatient perspective for some additional patients, obviously that's going to have a positive impact on patients and our budget."(P9)*

Clinicians were adamant that a second center developing a CAR T program would be beneficial too because it would create redundancy in the system:

> *"Eventually, I think we'll saturate Calgary and we'll have an inability to provide enough CAR T product to enough patients. So I think we will no longer be able to-- I think Calgary will be fully saturated and we won't have the capacity to offer anymore. So I think that's going to be the major issue and a second centre will be needed for more infrastructure to be built into Calgary, and my thoughts would be to have the second centre to allow for a bit more of a redundancy in the system to allow in the event of emergencies such as the coronavirus outbreak within one*

facility, at least you have the ability to siphon patients off to another center to do this." (P1)

From an academic perspective, although there was no FACT accredited cell therapy laboratory in Edmonton, there was the necessary infrastructure to manufacture a CAR T product:

"...and then I got introduced to [person] of the Alberta Cellular Therapy Manufacturing Facility of the U of A, and she set up a meeting between myself and [person] from Miltenyi going over decentralized production and particularly using the Prodigy. That's when the light bulb went on-- thinking here we had all the necessary resources and infrastructure to actually do this in Edmonton without having to rely on a pharmaceutical to be able to do this. And that's what really the incentive to go ahead was."(P14)

3. Access to Knowledge & Information

The individuals responsible for delivering the CAR T product were generally pleased with the ease of access to information. The clinical educators responsible for developing materials on teaching remarked that they:

"Oh no, it's a team effort, you know, like, it really is a team effort just with the information you guys have shared and with others that have shared and the reviewing that, you know, [individual] have provided and it is, you know, I think with this approach with education-- you get a better product that you can share and a better a more well-rounded approach…" (P4)

The clinical trial nurses involved in patient care also felt like they had sufficient information support from the study team were able to address their concerns quickly and efficiently:

"So as far as trials… they would have the nurses, the clinical trial nurses as a point of contact. But I think that [individual] did really good education with the nurses here in inpatient/outpatient setting, also at the U of A, and so I think just having

those resources has been really beneficial. I know [individual] has done a lot of work as far as just the patient education side as well. And so I think as a team, we've been able to, you know, it's still quite new, but at least we have a protocol for triage when they call. I think it's been pretty streamlined about who the patients need to contact if there's an issue that has arisen." (P9)

IV. Characteristics of Individuals

Knowledge & Beliefs about the Innovation

This section refers to individuals' attitudes toward and the value placed on the innovation, as well as familiarity with facts, truths, and principles related to the innovation. After identification and prioritization by physicians, clinical champions emerged to drive the process:

"And as well as part of the clinical implementation, I brought that forward in early 2018 to the subsequent provincial meeting, and I pretty much told Calgary I was going to do it with or without them. And I think that was persuasive enough to say that they wanted on as well for fear of missing out, I think to be honest." (P14)

Generally, frontline care felt the intervention was transformative and should be pursued. It was clear that excitement about the therapy did help improve frontline morale:

"I think they're excited to be able to put that learning into practice. And I think seeing the additional steps in doing the more rigorous assessments, people are excited to do this. And I think any time that we can bring in a new treatment that has such promise, people are excited to take part."(P9)

Self-efficacy

Self-efficacy is individual belief in their capability to execute courses of action to achieve implementation goals. By the time of delivery, the individuals responsible for pushing the

implementation of CAR T were nurses, many of whom were confident with the process due to its similarity with auto-HSCT (also captured in Trialability).

> *"Because again, we've done the autologous and we've done kind of that process for a very long time. They're comfortable with the actual infusion process, and I don't think that was too much of a departure from standard of care that we do with the autologous patients." (P7)*

Individual Stage of Change

The individual stage of change is the phase an individual is in as he/she progresses toward skilled, enthusiastic, and sustained use of the innovation. The individuals involved had participated in comprehensive training on monitoring and infusion prior to delivery, putting them in the final phase, in which little would change for individuals as the intervention became sustainably used. In assessing the program after the first few patients, the nursing manager said:

> *"And speaking to [nurse educator] about kind of the comfort level and checking in on the staff when we do have those infusions and for the first couple of days after just to make sure things are still going smoothly." (P9)*

Individual Identification with Organization

While physicians and administrators described attitudes and perceptions about the parent organizations of CCA or AHS discussed elsewhere, the nursing staff interviewed did not express any feelings on these subjects. Still, there was no evidence found to suggest this had on-depth sampling of practitioners could be carried out to ascertain these sentiments. Still, there was no evidence to suggest this impacted implementation.

Other Personal Attributes

The personal attributes of individuals involved in the implementation process (intellectual ability, motivation, values etc.) are the crux of the human resources-related facilitators of adoption. At the heart of these ideas is the motivation behind the clinical championship, which is built on a sense of moral obligation:

"I knew we had to try, and I knew that the right thing to do morally so I could sleep at night was just to support him as strongly as I possibly could..." (P3)

Furthermore, a sense of needing to undertake this work without expectation of compensation or recognition was embodied by the clinical champions and implementation leaders:

"Very few people will understand or appreciate what you've done. But you know, just it's the right thing to do anyway. So just do it."(P3)

The benefits of having motivated and altruistic staff presently, were also attributed to insightful decision-making by previous leadership that attracted intelligent clinical staff in the first place:

"Well, I think a lot of the success has to go to the fact that the guy by the name of [person 1] who used to be the head of the department here recognized [Individual 2]'s brilliance. And, you know, these kind of career discussions that early clinicians have-- looked at the opportunities. And this is why he went to [institution], right? We cobbled together some funding in a verbal [agreement] -- that when he came back, we'd hire him. And, you know, it all began with getting [Individual 2] here because that looked like the future, according to [Individual 1] and to [Individual 2]. And I don't know anything about the field to actually comment. It wasn't my idea, but I think it was brilliant. So the reality is, you know, [Individual 2] has moved heaven and earth to get this done, and he succeeded where virtually anyone else would have failed. And I knew he was far smarter than me and far more effective than me years ago. So I knew he was onto a good thing. I trusted [Individual 1]." (P3)

V. Process

In this section, I consider the effects of the adoption and implementation processes themselves, from planning and engaging to executing and reflecting. I also include the role of outside organizations that played a significant role in adoption, in particular the Foundation for the Accreditation of Cell Therapy, Novartis Pharmaceuticals Canada Inc., and the Alberta Cancer Foundation. These entities were primarily involved in facilitating access to the innovation, whether by directly providing it commercially (Novartis), reducing risk to organizations and promoting patient safety (FACT), or providing funding to support innovation and improve access on behalf of the patient community (ACF).

Planning

Administrators undertook the activity of assessing clinical need with the help of the clinical community and used this information to decide on the approach to implementation (multisite vs. single site) and develop a business case for additional funding. The administrator outlined it as follows:

> *"So any time we can take a provincial approach, I think it's well received and in many cases expected. So with Calgary and Edmonton, as you say, being in different places of readiness, the business case needs to talk through that. So if we were going with just one place, what would be the reason for that? When would we expand? How would we expand? So answering those questions along the way, I think, are important in the case as well, and if there's a good reason for it to only be in one place. And often that is the case if it's something really specialized because we're looking at, how do we provide that safe quality care that's still operationally feasible, sustainable and some of that gets down to minimal competencies and volumes of patients, that sort of thing. There's a certain amount of fixed cost infrastructure that's required. The more you spread out as well. And so trying to balance those off in a fiscally responsible way. So in the case for the CAR T seem to be a case to spread it out across the province, but also looking at where people were at, what kind of timeframes would it take to get everybody up to whole?" (P5)*

The decentralized manufacturing model was also brought up as an asset by industry in addressing the dispersed Canadian population with the unmet need:

> *"And I think that's one of the one of the unique things and one of the great things about Canada– is you guys have to think a little bit more creatively. You have to think about how as a community, we can support the person that lives in downtown Edmonton equally, as somebody who lives in you know small town Saskatchewan, right? You know, the rancher that lives, you know, five hundred miles or 500 kilometres away from Saskatoon has got a whole different thing going on. But at the end of the day, they still need the same quality of care and therapeutic options as somebody who lives in downtown Edmonton." (P12)*

Industry expressed that the process required for implementing went smoothly with their privacy assessment and other requirements:

> *"But again, Alberta is used to doing these, so they had somebody very proficient doing that piece of it. So we basically sat down as a team and said, these are the 20 things we need to do, and we had a meeting with the full AHS team and divided up the work. And so we have a pretty good workflow of all the steps that need to happen." (P13)*

Engaging

Opinion Leaders

The clinical community (opinion leaders) drove the implementation process and did not need to be engaged by administrators. It is well laid out from the chronology in the first chapter that physicians recognized the need for CAR T early in the process and were responsible for persuading leadership through every step of the process.

Formally Appointed Internal Implementation Leaders

A project manager was hired to drive implementation at the Northern site, while the other site added this role to the responsibilities of the implementing unit's manager. Speaking about the impact of the leader at the Northern site:

> *"I think it's a testament again to your involvement as well as [individual x] and getting things organized and from [individual x], from our perspective that you guys were very involved and doing the dry runs and making sure those pieces were in place prior to having our first patient. Just to make sure that everything went smoothly from initial, I guess, recruitment all the way up to that infusion." (P9)*

Champions

When asked if there was any process changes that could be made to facilitate improved translation/implementation of like products in the future, one participant said no, and that instead, the driving force has been and will always be tied to individual championship and leadership:

> *"... I don't care what the process is. You find a process or you make them make a process. And that's what I think [individual] has done together with his friends and colleagues who supported his vision. I don't think that there was anything pre-existing out there that really lent itself to this because you've got to get the university and you've got to get AHS and the ministry involved. Those things don't happen very often. It only happens if you've got a really strong message. So I don't think you can set up a system that will work for the next CAR T kind of big idea. These are too dependent on people and on leadership and championship to actually have a process in my mind." (P3)*

When applied to a particular example of a challenge in the implementation process, which involved engaging government in providing additional funding, two participants recommended an engagement approach built on simplicity and repetition:

"It doesn't matter what your personal feelings are about the government. It doesn't matter what your personal feelings are about the individuals. It doesn't matter whether it's anyone in AHS that you do or do not need to rely on. It doesn't matter the history-- all that matters is you get the funding--it saves the lives. And to do that, you have to give them credit and you have to thank them and you have to keep on message. And you can't mystify them with three letter acronyms and four syllable words, because these people are not as smart as you are and they're not certainly not as smart as Michael, they're probably not even as smart as me. You have to be polite and you've got to be able to explain it, and you've got to dumb it down and make it simple-- its simple communication, and you have one message and you hit it over and over again." (P3)

"What gets the money is when there's somebody willing to stand up and say you will save lives if you do this and you will save money if you do this-- you will lose lives and pay money if you don't do this-- you have to do this. And just and then rinse and repeat. And then the next day you say the same thing over and over again, except more loudly. Yeah, say that to everybody, you know, and keep on saying that and saying, you have to solve this problem. You have the money you could do this and you get all the credit. I'm happy to stand beside you and say, with your five million dollars of support for CAR T we will have saved probably 20 people's lives that otherwise would have died. And thank you, Minister of Health. Thank you, Minister of Health." (P3)

Attempting to engage the government and convey the opportunity from the upper administration of CCA, one participant reported a similar need to repeatedly put forward the same message until they became receptive:

"And then when we'd go and talk to government, we would talk about the importance of a Made-in-Alberta clinical trial, as well as standard of care and really try and relay what we heard from [individual] into the government people. So, you know, that seed was planted and it takes time for these things because you

can go in and you can say this, and you might have to say it three or four times before it suddenly dawns on somebody that ooh- might be a good idea." (P10)

"So that was again, just a lot of influence, talking, again, I credit [person], for a lot of that stuff but I think some of the others of us sort of sometimes I would think we were a little bit like, you know, there's Whack-A-Mole games you get at fairgrounds where the thing would come up and, you know, every so often we'd be popping up going "Made-in-Alberta CAR T, Made-in-Alberta CAR T, Made-in-Alberta CAR T" and I think there was almost enough of us around just every so often popping up that it finally got through to people's brains that the research and innovation piece in Alberta was something that government could go for, that they could get their heads around." (P10)

External Change Agents

These are individuals who are affiliated with an outside entity who formally influence or facilitate innovation decisions in a desirable direction. The outside entities identified in this study influencing implementation were industry and philanthropy, both financially supporting the development of CTP products. Industry motivated by time to market and profit chose a rollout strategy by which they engaged the site with the most advanced infrastructure and accreditation first and added more sites one by one:

"I mean, I think Calgary was picked one hundred percent because they were already FACT accredited. So that is full stop what it was. We were we made a concerted effort to first go to accredited again because we knew we had really high thresholds for lab audits and things. So it doesn't have anything to do with because I know some of our competitors don't need that need or ask for it. And again, we feel that we can relax that now that we're in major accredited sites, but our preference is still that they're fact accredited. So that's where we knew the Edmonton was going to be. And we said, well, you know, why don't we just work with them? And maybe the two things will happen around the same time." (P13)

This approach simplified the process of implementing from a company perspective, and it also allowed newer sites to learn from the lessons of other sites that came before:

> *"And so that was our strategy was work out the kinks of process because we if you do it well, then they can help teach some of the other sites. And so that's what we were trying to do was foster some mentoring between some of the other sites. So say Toronto SickKids as sites here we say here's a person versus it just being Novartis. We want them to talk to another clinical site and learn what some of their hurdles were and what they had to do overcome clinical, operational etc. And so that's what's been really successful. And that way, what we saw is that each site that came on could go a little bit faster. And so on the one hand, you've got your contracts and things, those are kind of off to the side. A lot of it that can slow it down is the really just the operational piece and are more staff needed to be hired you've got to hire them, train them all those pieces." (P13)*

As a result, physicians in Edmonton who solicited industry to provide their product were turned away as other sites got up and running:

> *"How to go about that was complicated, I had reached out to Novartis at that time, just because they had the only product that was nearing commercial availability, but was getting no traction there." (P14)*

Without a locally-manufactured alternative it may have been years before CAR T became available in Edmonton:

> *"I wanted to get in on the ground floor to be able to use it once NOC had come through. Novartis was resistant their restriction was that the sites had to be FACT accredited from a bone marrow transplant side of things. And at that point, we had only just started trying to submit for FACT accreditation, so we were nowhere close to that. They had identified two sites of administration, so one in Ontario and another one in Montreal. So as a result, we were nowhere in their scope as being*

a participant with standard of care, and they had no timeline for me either. So hence I was quite discouraged thinking that we would ever use Novartis product in the next two or three years after that. Fast forward two or three years, that's still the case now. So I guess we were right not to settle with them."

The ACF found the cost-effectiveness compared commercial products, potential for local access and aspect of provinciality all appealing:

"What they really respond to and how it really landed with me was--because we can manufacture locally, it's cheaper, less expensive, so it's much more cost effective and people can be closer to home, which is so important so they don't have to be in other centers for their care." (P11)

"The fact we knew there was a possibility of pediatric provincial-- like it really ticked a lot of boxes for the fact we're a provincial organization. The map was very important to us that we've integrated into our materials. This is where we have cancer centers. There's 17 of them. We know that CAR-T won't happen at every center. But the fact it happens in not just Edmonton, you know, the fact that there's Calgary, in fact that pediatrics component is there." (P11)

Furthermore, there was existing interest in the community reflected by healthcare administration:

"...it was something that Alberta Cancer Foundation certainly likes to, um, not identify but support projects that we hear of interest to the community that are also recognized in the health system as a priority and matching those too. So I feel that this is a perfect example of a project [with] donor interest and curiosity, and many donors were leading that conversation, asking what we were doing in this sphere. And I think that helps to drive some of the conversations with the health system. Say what, what is going on or how could we help in this area?" (P11)

As such, the ACF essentially catalyzed the process of implementing CAR T in Edmonton by supplying the initial donation that would go to hiring a formally appointed implementation leader:

> *"ACF actually was, I think, the catalyst for the CAR-T trial because they were willing to put money on the table first. So they put the idea of money on the table before AH and AHS had committed. But they were very clear in saying that they couldn't release anything until other people came in and said, yeah, we're on board, right?" (P10)*

It was the initial role then of the clinical champion and the internal implementation driver to secure collaboration between the remaining stakeholders leading to new relationships and pathways for future innovation; according to the facility, a medical director:

> *"I think it's at least in my, my experience, a novel thing because you had collaboration between the foundation who put it a significant chunk of the money, the cancer program, the non-cancer health care system and government to be able to move this forward. I mean, that's incredibly complex and to try to get everybody to get on, get on side with that, that's what took so long... So I think that's probably the biggest thing. Now you have relationships and pathways and [you can] say something like this can be done and this is how we did it. So I think that's probably one of the big lessons." (P6)*

Executing

Key Stakeholders

There were many stakeholders involved in the process of implementation. Individuals from the departments of BMT, apheresis, clinical trials, inpatients, outpatients, laboratory, pharmacy and diagnostic imaging were all involved contributors to the success of implementation at both sites.

Key individuals behind BMT, clinical trials and CAR T groups contributed to timely and smooth implementation.

> *"Again, we're very fortunate, I think, to have the team that we do and to have the individuals behind both BMT, clinical trials and CAR T that we do because I think regardless of the fact that we were dealing with multiple competing factors like you said, such as FACT, CAR-T, the pandemic all at the same time, I think it still went relatively smoothly. Things were remaining on track and we were able to still proceed with the FACT inspection on general-ish time given the constraints of the pandemic. But I had no concerns. It all went as smoothly as I think it could have." (P9)*

For the implementation of investigational CAR T, additional approvals were required compared to adopting a market-authorized product:

> *"The problem with the trial is because it impacts so many different people, you have to-- it adds complexity in terms of trying to get the trial approved in terms of who you get, sign off on because you have to involve people that are outside what we traditionally do to sign off on our clinical trials are impact analysis is usually just signed off locally, whereas with a CAR-T trial, you have to get sign off by all these other all these other areas too." (P6)*

Innovation Participants

The innovation participants are those served by the innovation (i.e. patients), and their sentiments were reported by the nurses interviewed. Nurses felt that provision under a clinical trial allowed for a closer relationship, which patients enjoyed:

> *"So knowing them kind of from start to finish has been-- I think the patients have a lot of confidence in our skills. And then it's I think it's really nice for them to have that one person that they can contact and then we can kind of coordinate their care. I think it's made a much easier process than having multiple people involved and*

just having that one person or the one team. So the CTNs that we can contact [individual], we can contact, you know, fax prescriptions. We do all of their assessments. And I think it does make our assessments quite a bit more tailored to the patients." (P7)

"They said that point of contact was really important to have one person that they can call about scheduling all of those things. It's been really helpful that they made the CAR-T, that patient education sheet because what they what a lot of patients have said, it's really hard for them to explain to others what CAR T is, and obviously it's a highly clinical procedure, and so it's been really helpful to have that kind of document that we can give to them and that they can explain to their families and friends and loved ones about what's happening." (P7)

Trial patients reported a sense of altruism in contributing to clinical research and helping others:

"So they all had very aggressive disease. So that's one of the big things. They all were relapsed or very refractory to any treatment that we provided them, especially the lymphomas. They just nothing really seemed to work. I think by having the opportunity to be able to participate in this trial, especially, it's a phase one was very important to most of the most of the patients that I spoke with just because they know that they are able to help others by doing this. There were some I found with these patients there was definitely an altruistic vibe to participating as well, you know, of course, they were hopeful that it was going to work for them, but also the fact that they're helping with the further research." (P7)

Lastly, patients were happy to be able to undergo the therapy closer to home:

"I think most of the patients have been very thankful that they have been able to have this happen in Alberta or in our center. The patients who have gone out of province or out of country have said it's been a very different experience than having it here at the cross, just because they're going to different doctors. They

don't know the nurses there and they're kind of transferred back here post. So it's a little bit of a different process. Like, I spoke with a few that had their CAR T out of province and out of country, and they said it was pretty anxiety provoking because you just don't know what to expect and you don't really know who to call and then you kind of get transferred back here. And so I think just having everything in-house has been beneficial for that reason." (P7)

Reflecting & Evaluating

Nursing was heavily involved in the implementation of CAR T and when asked to reflect on the results, identified the retention of staff post-pandemic staffing as the biggest issue going forward:

"I think the biggest potential roadblock that we're going to run into and who knows what that looks like post-pandemic in terms of staffing levels, that's going to be potentially be the biggest roadblock. And I think that that's going to transcend nursing as well and go into your other health care professionals as well, right? Your physicians, hematologist, all those pieces." (P9)

"I think some of the HR challenges are more recent, so I don't think that there was a significant impact on us starting this process. So at least that was a positive. I think the biggest challenge moving forward is what healthcare is going to look like post-pandemic." (P9)

"It's too terrifying to even think. Yeah, honestly, it seems like there's going to be a mass exodus from health care, whether that be from burnout, different opportunities elsewhere. We're already seeing that, and I was actually listening to a podcast that was talking about pandemic flux syndrome and just the results of that and what that means for everybody was actually quite interesting." (P9)

In terms of further sustaining the program itself, a high level administrator identified the need for promotion by the organization, not the champion:

"And [person] is not the world's most ambitious self-promoter, he's going to undersell what he's doing. And I, he's not a used car salesman, and I think you're going to need somebody on the team that's going to do that for him." (P3)

Patient experiences as reported by frontline workers were positive, especially those enrolled in the clinical trial:

"I think the patients are excited to be able to partake in this process and the ones that I have spoken to, they're just, you know, grateful to be able to be a part of the trial and to be given this opportunity and to, I think, partake in it. So I haven't heard anything negative, which is good. And the process, they said as well has been quite smooth for them." (P9)

"Once the process started, though, all the patients said it was very, very well structured. The planning was very easy to follow. They said that point of contact was really important to have one person that they can call about scheduling all of those things." (P7)

In terms of evaluating the program, difficulty in counting the costs were identified as a challenge despite the short length of follow-up to date:

"And then someone's going to have to go through it and say, well, how many of these were related to CAR-T and how many were related to-- patient went to a doctor for something else? So the majority are going to be CAR-T related, but it's retrospective. It's a retroactive look instead of a prospective, one which again, is what the traditional health care system does. It's usually done afterwards because that's the way they've done things, whereas in a trial when we submit the test. So if I need a CT scan, it says for this clinical trial and the trial number's stamped on it. So DI sends in the invoice with that number on it. And so it gets tracked to the trial, so it goes to the right area and the same with lab." (P6)

Clinicians recognizing the potential cost-savings for the system reported no process for appropriately making recommendations upward into administration:

> *"So being that CAR T-cells are currently approved of what our clinical trial is is a third line and beyond. If we move that up into the second line, certainly that opens to more patients number one, but number two potentially adds cost to the system, especially if we use standard of care-- but if we used our product, that would actually be cost saving, on the order of potentially millions." (P14)*

Furthermore, at this point, the current demand well outstrips capacity even with the additional funding from the grant:

> *"...there's much more demand than what's been approved in the grant. In fact, we're even hearing that from government. They're saying, Well, we want you to start thinking about taking on out-of-province patients, well we can't we only have so many we can do. We only have approvals to do so many. And even if you gave us the money to do out-of-province patients, we don't have the resources and we would need to open more beds." (P6)*

In terms of positioning the organization for the future, the adoption of CAR T has shone a spotlight on Alberta's position nationally. The introduction of ACT-C01 has cut a path out of the cycle that can trap smaller institutions: below average infrastructure and human resources leading to difficulty attracting talent, leading to less experience, causing less interest from pharma in being a site for clinical research, ultimately growing the divide between innovative and standard care resulting in worse infrastructure, restarting the cycle. If properly managed, the successes being realized now can form the foundation for future innovation and foster a return to the cutting edge of biomedical innovation:

> *"If you know, wait another two years, this will pass us by. We won't be able to attract the best and the brightest, and we won't be able to, you know, it's like surfing.*

When you're on the crest of the wave, right? You've got you're going to have momentum. And if it passes you by, you're just in the doldrums." (P3)

"...this is where the future is going to be if we're going to have any flexibility because this is just, you know, CAR T 1.0. And you know, the new data are suggesting there are new and better therapies coming down the road, which will be as or even more expensive and include solid tumor populations. So we've got to get in front of this or we're just going to get swamped." (P3)

One clinical CAR T lead mentioned it remains difficult to continue improving the program given the current process for innovating:

"Certainly I would probably go through the same project manager again and try to chase that up the chain, but whose actual responsibility it is to make that happen? …So temperature tracking, preventative medications such as Anakinra for IL-1 inhibition, tighter managing over the weekends-- you know, having a 24/7 touchdown space, being able to give tocilizumab on the drop of a hat at any time of the day as an outpatient again delivery, given that it's only a one hour infusion. All of those are things that we could easily do to keep people out of hospital, but things that aren't easily done at this point in time." (P14)

Discussion

The most pervasive challenges were those related to the innovation and the inner setting. These were overcome by innovation characteristics like the perceived relative advantage of the technology and the characteristics of individuals, especially the motivated, collaborative and determined clinical community. Known C/F to CAR T provision identified by other groups in the literature were also observed in this study, including the perceived and actual complexity of implementing the innovation, lack of hospital resources and funding as challenges, and

decentralized/ point-of-care manufacturing as a facilitator to timely access to treatment.

We found that autologous, patient-specific manufacturing, a hallmark of CAR T to date, has led to increasing industry control over drug access. Furthermore, many of the canonical challenges are interrelated or nested, suggesting a need for new methods of ranking of challenges hierarchically to better evaluate their impacts, allow policy researchers to most efficiently propose strategies to address them. In so doing, and with concerted changes across the ecosystem, challenges to translation, adoption and implementation may be overcome providing better outcomes for patients, conditions for providers, more choice for administrators and a more efficient system for the public.

Product Cost

A commonly reported barrier to adoption is product cost[66–69]. While this is true for payers and pricing negotiation, I contend that once the decision to adopt is made by health system executive, there is little effect of per unit cost on adoption at the administration level or below. A high product cost may preclude products from getting to that point, however in this circumstance, both products had crossed over that hurdle rendering this a moot point. How governments and payers will react when they begin to see a rise in costs of provision as indications expand, remains to be seen. As costs rose in the US the Centers for Medicare and Medicaid Services (CMS) opted to reimburse US hospitals for up to 65% of the product cost leaving them to recoup the remainder plus associated care costs from the patient or private insurers[70]. How outpatient provision will affect the reimbursement and product cost of CAR T in the future is also a salient topic in need of further investigation.

Bench-to-Bedside & Industry-Controlled Drug Access

Discussed as an operational issue, the administrative resistance to implementation caused by the challenges of patient-specific manufacturing are often over-exaggerated by researchers[6,21,71]. For implementing centres like these with well-established HSCT programs with access to apheresis most of the procedures required are easily adaptable, including those for collecting PBMCs when coupled with published literature on lymphapheresis to bridge gaps[29,31,72]. To address logistical challenges, updated computing infrastructure and training may be required as directed by the

CTP supplier but these challenges are soluble and singular. HSCT programs have document tracking system for maintaining chain-of-custody during transport, however some additional shipping containers may be required. Some additional coordination requirements may be levied on BMT units, however these can be solved by expansion of existing roles. Once the CAR T product is received and prepared, its administration is simpler than a relation to HSCT or chemotherapy infusion. An often cited recommendation or challenge is that of training of staff and implementation of new procedures. I acknowledge this is a challenge but in relation to access and funding challenges, these are soluble and easily overcome with proper harnessing of the eagerness of frontline hospital staff.

Considered as an access issue, the effect of patient-specific manufacturing is a keystone challenge (one upon which many others depend). From a quality perspective, industry will necessitate their involvement at the hospital level to ensure products meets specification and are transported under appropriate conditions. Regulators also require industry to interact further with clinical sites prior to and also after market approval by mandating the inclusion of a risk evaluation and mitigation strategy (REMS) for clinical centres[73] in the United States. These two sources novel interaction coupled with the supply constraints brought on by centralized manufacturing ceded an unprecedented amount of decision-making power to individual CTP suppliers. In practice, these new roles force industry to carefully select initial sites based on infrastructure, accreditation, and logistic support and then sequentially rollout the innovation across the country, determining which sites get access to the therapy and when (at a slower rate than with small molecule drugs and monoclonal antibodies). Depending on where industry decides, patients may be forced to travel great distances to receive care (preventing access for some and forcing others and their caregivers to take on a large financial burden)[74] and allowing for patient condition to deteriorate while waiting for an industry-set manufacturing slot.

Once implemented, industry then determines access on a patient level by control over limited manufacturing slots. Unnecessary additional transport time back and forth from the manufacturing facility also contributes to worse patient outcomes and more severe adverse events. At the hospital level, industry now inadvertently forces centres to spend in pursuance of accreditation, build additional infrastructure and request funding for additional human resources

even mandating and monitoring some standard operating procedures and reporting practices. The net result of this greater role of industry borne out of patient-specific manufacturing is higher costs to payers, less control of patient care for physicians, more expenses for hospitals and a widening access gap for patients.

Decentralized Manufacturing

In the long term, decentralized manufacturing can offer a route toward quickly providing better patient and health system outcomes, a superior access alternative with improved cost-effectiveness, and economic stimulus. In pursuit of these goals, academic institutions, philanthropic organizations, and government have taken steps to reacquire control of development and access to biologics in Canada through collaborative initiatives[75] that lead to projects like ACIT001/EXC002. Locally produced products like ACT-C01 and CLIC-1901[76] show that small and medium research teams funded initially by philanthropic donors can bring promising therapies to the clinical that can compete with similar products sold by pharmaceutical companies.

A decentralized approach could get more centres online faster, allow them to tailor manufacturing approach to population, bring control over drug access back to clinicians and those invested at the frontlines of care, allow for closer coupling of need and manufacturing capacity (lowering cost), reduce patient travel, and shorten time to treatment for patients[77,78].

Point-of-care Manufacturing

Delivering innovation as product manufactured through an institution (hospital or university) returns the control of access to the technology back to clinicians, offering a range of possible benefits (customizability, shortened time to delivery, clinical and manufacturing capacity coupling, and product development)[20,79,80]. The benefits that can be realized for the health system through further development and implementation of POC CAR T is a major enabler that can go unused. Frontline staff and innovators are aware of the potential benefits but have difficulty generating and organizing the data needed to persuade middle management of the potential utility. Depending on the hospital, new integrated systems for tracking the costs incurred by

departments in the provision of CAR T may be needed to demonstrate the added value of adopting the technology when combined with existing outcomes reporting. Such systems would need to be manned and operational during the clinical research phase to collect this data optimally, something that clinical research units are not responsible for, or motivated to undertake presently. Funds from the business case should be available for this endeavour at both sites, potentially under the umbrella of the Quality Assurance/Quality Control arm of the HSCT programs. With the introduction of EPIC well under way in Alberta, a wealth of data that could be used to optimize patient selection, starting material acquisition and aftercare will soon become available. Proper collection and analysis of such data would also be useful in demonstrating the comparative value of each technology across sites and on a national level, which may be of interest to government and payers as indications for CAR T expand into earlier lines of therapy and other conditions.

One drawback of the approach is that institutions are exposed to potential legal challenges from pharmaceutical companies holding these patents-- and will continue to do so for over a decade (the original Penn patent protecting CTL019/Kymriah does not expire until 2034)[81,82]. Regardless, given the idiosyncratic nature of the manufacturing method, vector design and cell culture processes there is room for innovation that could side-step this issue and generate a potentially superior product. Due to the nascence of the approach, none of the POC CAR T products have yet been commercialized and is unclear to what extent pharma will move to legally challenge these new companies. Further analysis of the intellectual property issues around CAR T is beyond the scope of this paper and has been reviewed elsewhere by legal experts[14,83,84].

CAR T and new types of cell and biologic therapeutics will continue to succeed in the clinic. It will continue to move up the lines of therapy, replacing auto HSCT in lymphoma and myeloma becoming standard of care in these populations. As such, hospitals will need to step up and radically change their approach from treating patients with surgery and chemo radiation to immunotherapeutics and biologics. More patients will be treated in the community, and the responsibilities of clinical lab, pharmacy and inpatients will need to adapt. Future-looking hospital management that balances the funding of these departments during this shift will be

crucial, and health system administration should be held responsible for their failure to pre-empt system need and secure the appropriate resources for clinical staff.

Federal Regulation

By regulating CAR T as a pharmaceutical[23,67], CTP developers are forced to secure enormous amounts of capital to commercialize their technologies (a large portion of which is paid to clinical trial units or contract research organizations for clinical resources) even if they only intend to provide them at local institutions with the same teams at the same scale they did in their early-phase trials. With decentralized manufacturing infrastructure growing across the country[85] and researchers collaborating[75], regulators must now play a part in reducing the burden on the commercialization of these technologies. The most effective path to this outcome is to acknowledge the long term safety data on third generation lentivirus transduced CTPs[27], and update Canadian regulations in a similar fashion to those in Europe that exempt point-of-care produced and administered products from the Food & Drug Act legislation[69]. Health Canada regulators are aware of the issue and the possible solutions as reported in their 2020 policy position paper[87], but to date, no revisions to their regulations have been made. Introducing regulation like that in the EU would reduce the financial burden on developers, reduce costs to hospital and eliminate lengthy clinical translation timelines allowing for the fastest access to cutting edge drugs possible[42]. Regulation by the New Substances Notification process of Environment Canada was also redundant and needlessly time-consuming, showing concordance with another published article with the same finding[88]. Nevertheless, if Federal regulators act quickly and in concert with the clinical and research communities they could realize tremendous potential for years to come from this opportunity to modernize.

Hospital Resources and Funding Structures

Cancer remains the leading cause of death in Canada[89] and the incidence of the disease continues to rise year over year[90]. While improvements in treatment have come at an exponential rate in recent years, Alberta's oncology healthcare infrastructure lags significantly behind. Physical infrastructure, constraints inadequate clinical funding, and now human resources shortages remain major issues at each site. The CCI site has not received investment toward inpatient bed capacity since it opened over fifty years ago and according to the Health Minister in 2018

speaking at the fiftieth anniversary of the building's opening, there were no plans to replace the facility at that time although incremental infrastructure investments would be made as needed[91]. A shift toward outpatient care[92] will be extremely beneficial to avoid an infrastructure/capacity induced bottleneck in Edmonton as CAR T becomes SOC in second line for NHL[93]. An American economic evaluation of outpatient delivery reported a ~$32,000 reduction in total costs per patient using this approach[94,95].

Although physical capacity was also an issue in Calgary, with a new $1.4 billion dollar facility opening in 2022[96], limited funding and human resources at the FMC was the bigger issue. As a result, both cancer centres have relied increasingly on services provided by the larger general hospitals (FMC and UAH), which likely contribute to the strained relationships between hospitals when it comes to sharing resources and beds.

In the early stages of implementing a technology, especially one with as a varied resource impact as CAR T (in its current iteration), a commitment to the short-term sharing of resources between departments is crucial, especially for smaller centers that utilize the services (i.e. apheresis) of other departments/hospitals. Obstinacy at the managerial level and above is exacerbated by apprehension around the challenges to implementation of CAR T or similar technologies and puts unnecessary stress on clinicians trying to provide access for their patients by making them into system level advocates, a non-traditional and novel role for many physicians. In cases where reticence ends in a refusal to provide care until more funding is made available, a lengthy delay can result, especially in provinces where multiple levels of bureaucracy exist between the funder (ministry) and the hospital, as was the case when CCA assumed the responsibility for requesting additional clinical resources. If departmental management insists on protectionism and cannot be made to cooperate by upper management projects will be delayed and patients will suffer.

In this particular case, it was the considered opinion of several participants in the clinical stakeholder domain that the approach taken to acquire additional clinical resources was opaque, crude and surreptitious; and the following review processes ad hoc, inefficient, redundant and shamefully time-consuming. Moreover, the funds and resources hastily and unceremoniously presented to management were either inaccessible or insufficient to meet the current, let alone

future demand. It is clear then, programs could have been launched at the same scale with existing resources while the clinical funding request was reviewed. From a process perspective, the fact that a single hospital administrator was able to halt adoption of a potentially curative treatment for over a year, province-wide, by triggering funding requests and reviews so redundant and ineffective they required approval from both the CEO of AHS and the Minister of Health, while terminal patients expired or left the country for treatment should be a poignant warning of the state of the healthcare system and a shameful display of negligence. Moreover, these results are an example of consequences of the reactionary and evasive attitudes that pervade both AHS and CCA, which obstruct innovation, burn out staff and waste resources — all enabled and perpetuated by unnecessarily bureaucratic, impractical, and self-serving organizational hierarchies. Nevertheless, in the face of all of this, physicians and nurses struggled to overcome these challenges with the support of external agents. Let us keep in mind that CAR T offers a terrific opportunity to assess the state of play in cancer care and continue uplifting Albertans in the face of this emperor of maladies.

Research Team and Reflexivity

The primary author conducted each interview as part of their MSc thesis research, which also included an historical review of the clinical adoption of CAR T. During the time of the study, they were employed by Cancer Care Alberta, Cancer Research & Analytics as a project manager of the clinical trial ACIT001/EXC002 (NCT03938987) and were one of the two initial members of Alberta Cellular and Immunotherapy (ACIT). The primary author has work and experience in a clinical oncology research specializing in lymphoid hemato-oncology. Prior to this study, they had worked as an inpatient unit clerk at one of the study sites from 2008-2014 while completing a BSc in Biological Sciences. Additionally, the author contributed to original research on the global clinical translation of cell therapies. The interviewer had also previously conducted and participated in other qualitative research studies that included interviews, and had been trained in these methods in the School of Public Health at the University of Alberta. Eleven of fourteen interviewees were acquaintances or colleagues of the author prior to the study. Due to the author’s proximity to the unmet need in this population, they come from a position of advocate for CAR T implementation.

Limitations

We were unable to secure participation of any individuals with a payer/government affiliation. As such, additional insight on the impacts of pricing negotiations and the drug HTA process was unavailable. With regard to the information on FMC/TBCC or ABMT, we were unable to secure a nursing perspective that may have illuminated the institutional preparations at the Calgary site. I acknowledge there may be sampling bias as a result of the two clinical sources, however these individuals were both directors of the program and contributed greatly over the course of the implementation period. This is an unavoidable by-product or studying a specialized innovation early in the diffusion process. CAR T is also indicated for a pediatric population and I acknowledge the lack of pediatric perspectives in this study, however, it should be noted that at the time of data collection, CAR T had not implemented at either SCH or ACH in Edmonton.

The findings of this study are generalizable across sites and systems considering adoption of CAR T, becoming less germane to adoption of simpler technologies in other indications. The generalizability is limited by the close relationship between the innovation and the conditions, specifically the autologous nature of the therapy and unique aspects of oncology healthcare. However, the lessons are broadly applicable to other expensive, patient-specific therapies that provide a considerable relative advantage over current standard of care. Many C/F we identified were also related to prior conditions such as hospital infrastructure and available resources which are factors that implementation for all technologies delivered in the inpatient setting.

Regarding follow up, the study was undertaken only 5-6 months after launch limiting the extent to which implementation outcomes could be assessed. The patient experiences reported should therefore be considered as exploratory only and not offering any concrete utility in determining patient tolerance to either CAR T product. Nevertheless, initial data is promising and this area should be explored further, perhaps along with the economic comparison of the two products. Lastly, at this point each site had only implemented one of the CAR T products, which precluded direct comparison of two products at one site, however we expect this to change in the future.

Conclusion

CAR T is a platform technology with the potential to transform care in cancer and other conditions. It has achieved astounding clinical successes by the third iteration, becoming a routinely used curative-intent therapy in a previously uniformly terminal population. It follows that expeditious adoption, development and implementation directly contributes significant improved patient outcomes and should be a major priority for the clinical and administration communities moving forward. How to optimize this process is an area with little available literature, especially studies that contain with real world evidence. Studies of this nature are precluded by many issues including the sequestered, defensive and guarded nature of these organizations. Using a case study approach, I confirmed many of the challenges and facilitators reported by other researchers were at play during the adoption process, building on this by describing the C/F in detail and how these varied by site, preserving these lessons in organizational memory.

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Appendix 1.2: Master Interview Guide

Focusing Questions

1. What was your role in the introduction of CAR T in Alberta/clinical site?
2. What were the key challenges specific to this type of therapy?
3. How does the introduction of CAR T differ when compared to the introduction of other innovative technologies in oncology?
4. How did the differential infrastructure and past experiences in Edmonton and Calgary impact the introduction of CAR T in Alberta?
5. What were some of the successes in the implementation of CAR T in Alberta, and how do you think the implementation process could have been improved for future technologies?
6. What role did the business case play in the introduction of CAR T?
7. What pathway did the business case follow after it's submission to Alberta Health?
8. How was the decision made to pursue implementation of commercial product in Calgary and Academic product in Edmonton?
9. How did the following factors affect this decision:
    a. Accreditation status
    b. HSCT programs
    c. Selection by sponsors
    d. AHS leadership decision making
    e. CTL for product handling and prep
    f. Role of pharmacy
10. How did there come to be an IIT and commercial product implemented nearly simultaneously?
11. What additional infrastructure was required to implement CAR T in a research and commercial context at the TBCC?
12. Could you describe any collaboration between other sites in the implementation process?
13. Which tasks were shared and which were unique to each trajectory?
14. How did these factors interact to produce timeline for each trajectory?
15. What are the results on final process and outcomes of each approach?

16. How could the implementation process have been improved to better serve Alberta patients?
17. What were the major challenges to implementation of each product and CAR T in general?

External Factors

18. Fludarabine shortage
19. COVID-19
    a. University shutdown of manufacturing prior to VR1 and VR2
    b. Miltenyi tech to perform software update delayed
    c. Health Canada CTA review time period extended
    d. UAH ICU constraints
20. EPIC/Connect Care
21. Human resources

Clinical Trials/Development

22. What is the status of implementation of commercial CAR T products at the TBCC?
23. What is the level of access to CAR T for ALL and NHL for Alberta patients currently
24. Are you able to send patients to other centres to receive this therapy?
25. As a center that has prepared for CAR T implementation what was required in terms of infrastructure, SOPs and could you outline these tasks in order they were completed?
26. How does FACT accreditation influence the process of CAR T implementation?
27. Having now provided CAR T at the TBCC under a clinical trial, has there been an increase in resource utilization? Which services or departments were affected most?

Clinical Factors

28. What do you expect the future indications of CAR T for NHL and ALL will look like
29. Are there any delivery or implementation issues that you anticipate are unique to Alberta or Edmonton?
30. To what extent will the delivery of chimeric antigen receptor T-cell therapy require additional staff or training?

31. What would be an ideal system to manage outpatients who have responded to the therapy, but could still experience toxicities?
32. How have the unique side-effects associated with chimeric antigen receptor T-cell therapy affected the implementation of these products at the (site)?

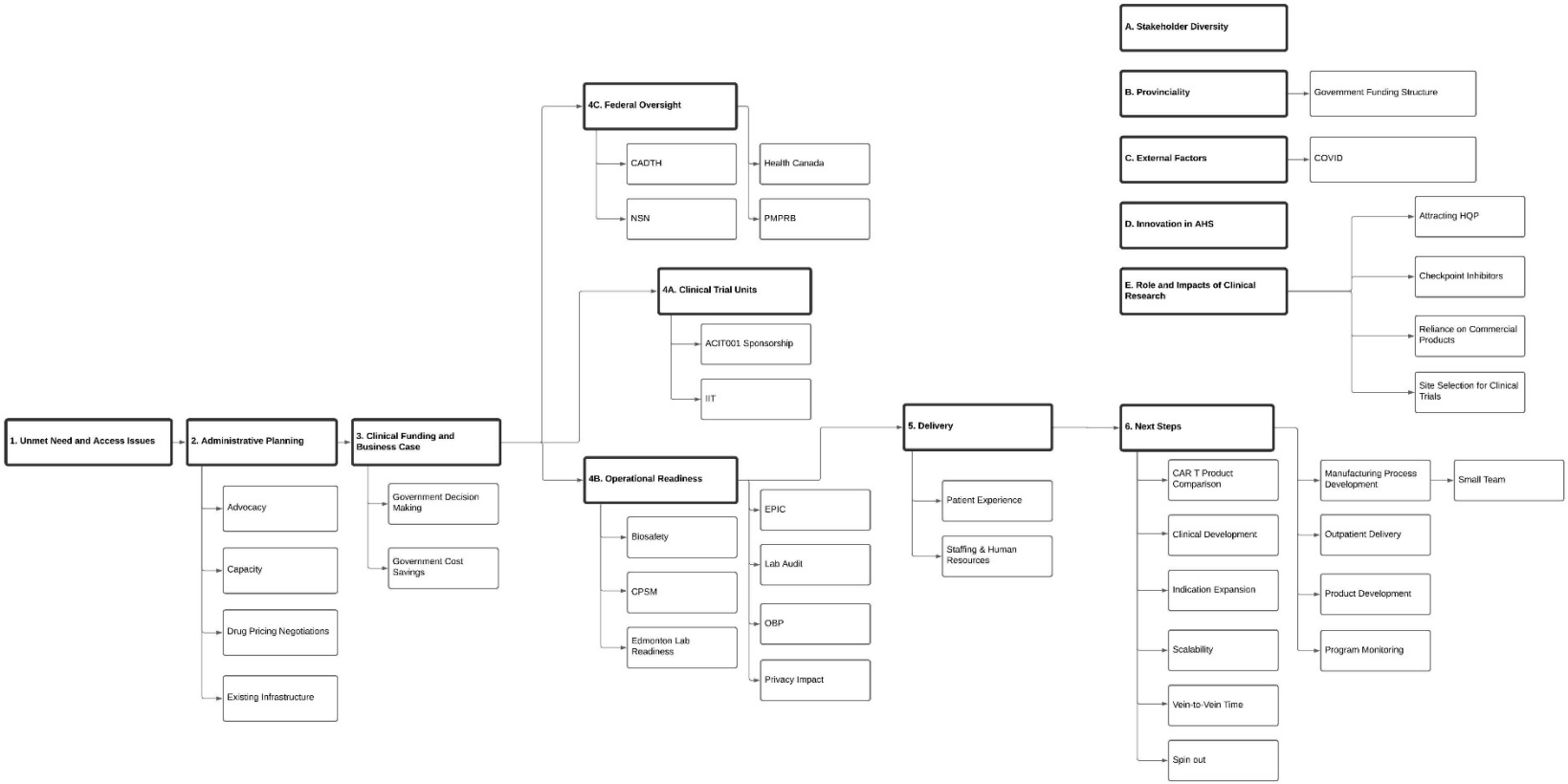
Value Assessment/Funding/Policy

33. Experience with the business case and were those resources sufficient
34. If chimeric antigen receptor T-cell therapies are reimbursed using a leasing model or performance based pricing structure what party should gather effectiveness data, and how should this information be collected?
35. How has the AHS leadership perception of CAR T changed prior to and after implementation?
36. What is planned in terms of monitoring the CAR T program in Alberta going forward?
37. How was the governance structure for CAR T implementation chosen and has it been successful in its goals?

Miscellaneous

38. Do you know of any individuals that have expertise on any of the topics above that would be willing to participate in this study?

Appendix 1.3: Coding Tree



Appendix 1.4: Measures of Optimal Innovation Adoption

Implementation Outcomes	**Service Outcomes**	**Client Outcomes**
Feasibility	Efficiency	Satisfaction
Fidelity	Safety	Function
Penetration	Effectiveness	Symptomology
Acceptability	Equity	
Sustainability	Patient-centeredness	
Uptake	Timeliness	
Cost		

Appendix 1.5: Supplementary Discussion of Implementation Outcomes

Proctor et al. proposes a series of metrics to measure the success of implementation that are pertinent to the topic and together with our results can be used to suggest avenues for future research. *Feasibility, fidelity, cost, penetration,* and *sustainability* are the implementation outcomes of concern we identified as particularly relevant to this innovation and we discuss them below as they relate to the challenges and facilitators presented in the previous section.

While mentioned only briefly in provider interviews, frontline staff felt the interventions could be delivered in a fashion that they found 'suitable for everyday use' meeting the *feasibility* outcome (at the current scale), whether it is appropriate for future demand is not assessable with this data. The implementation outcome *penetration* is similarly moot, as both major centres have now adopted the intervention and may be considered 'fully penetrated'. As a topic for future research, frontline providers could be interviewed on new ideas to optimize the new processes and procedures. The *fidelity* of intervention is more difficult to assess and requires clinical data and longer follow-up, however we believe that the human resources required to generate and analyze the data already exist; clinical trial staff and sponsor researchers in the case of ACT-C01, and BMT QA personnel in the case of Kymriah at FMC/TBCC. It is simply a matter of comparing the results, and would prove a valuable line of inquiry to hospital or health system administration.

From a patient and provider perspective, time to delivery and therapeutic effectiveness are the two most concerning metrics. It is clear from the indication that effectiveness is paramount but this parameter is essentially fixed by the point of early-phase trials, (aside from exceptional instances like ACIT001/EXC002). Time to delivery however can very clearly be optimized both during the pre- and post-adoption phase. Before the drug is available at the providing institution, better coordination between governments is needed to ensure access for patients is not impeded by lack of reciprocal funding agreements between provinces while offered under clinical trial. After the decision to adopt has been made, systems for acquisition of additional clinical funding should be better outlined and developed, with an eye toward *sustainability* and proactivity. Doing so would help rebuild trust between parties and lend credibility to future assurances that

hospitals will receive requested resources in a timely manner and be able to use them quickly when CAR T programs expand. Improving those relationships will undoubtedly accelerate implementation for future technologies. A possible enabler is the collection of real world data on cost and effectiveness by hospitals, which is timely when paired with the simultaneous implementation of digital EMRs at many sites.

We highlight collection of outcomes data as an area of need and an important area worthy of future investment. Akin to the collection of effectiveness data is that of cost data, which is already being tracked due to the grant-like funding structure of the program during the initial three year period. The cost of care was of particular interest to hospital administration and is already being collected. Ensuring that this data continues to be collected for each patient receiving a CAR T product across sites is of the utmost importance to a complete and accurate valuation of each approach to the program. Given that the price of ACT-C01 is covered by the sponsor during the clinical trial, compared to payers in the case of Kymriah, from a health system perspective, the academic approach is vastly cost-saving. With comparable effectiveness, the ICER between the two interventions would be considerable.

Of all the metrics, *sustainability* ultimately determines how accessible CAR T is to patients in the future. Provision of CAR T through clinical trials is attractive to patients and providers for its timeliness, customizability, separation from the bureaucracy of AHS, and the patient-centered care that comes with properly managed human resources. However, in the case of ACT-C01, with the provision under a clinical trial, the keystone stakeholder group in providing access to therapy is the manufacturer ACTM, who, unlike the clinical community, is motivated not by altruism or fiduciary responsibility. Unlike pharma, they are not motivated by profit, as they are to some extent insulated from financial burden by the parent organization, the Department of Surgery. As an academic entity, the primary force animating ACTM and its management is academic achievement measured in publications, an end that fundamentally conflicts with the goals of the clinical community which wishes to see production scale-up as quickly and efficiently as possible to meet unmet need. It is now clear that a new and distinct commercial entity with staff incentivized financially is the best method to provide CAR T on an ongoing basis in the most clinically effective form, and most efficiently at the required scale.

With ACIT001/EXC002 expected to close within three years, access to ACT-C01 will stop without commercialization, regardless of its relative advantage to Kymriah or other commercial CAR T products. In that case, millions of dollars of investment by philanthropic organizations will be wasted and Alberta will have lost another locally developed health technology to the translational "valley of death"[97–99] that is also winning the battle against two other University of Alberta interventions: pancreatic islet cell transplantation for Type I diabetes mellitus and fecal transplant for patients with recurrent and debilitating *clostridium difficile* infection. It is now prudent for health system administration and academic institutions to come together and prioritize the support of technologies we have already invested so much in developing, to continue building a bio therapeutics industry for Albertans.

Chapter 4: Taking up Serpents: Adoption of CAR T in Alberta

CAR T is a unique, expensive and logistically complex modality that now yields curative outcomes in previously palliative populations[1–3]. It also arrives at a time of profound change in healthcare: the culmination of decades of basic science research and investment by pharma; increasing investment in biotech by academic institutions and the public sector; a burgeoning role of disease-specific patient groups in funding research, a shift away from small molecule drugs and broad indications toward biologics, biosimilars and patient-specific therapy; a growing elderly demographic in the developed world; and increasing pressure on payers from high cost drugs[4–6]. These factors interacted to determine how CAR T was adopted in Alberta, a detailed analysis of which is provided through this study with the intent to preserve these lessons in organizational memory.

This innovation provides a rare opportunity for researchers to test how quickly and efficiently the healthcare system can adopt a transformative innovation, allowing them to identify where and how the system may be improved to produce better results in the future to the benefit of clinicians, patients, and the public. Due to the nascence of the field, however, a dearth of literature on the real world adoption of patient-specific cell therapy products exists, especially perspectives from leadership and administration in publicly-funded healthcare systems. I hypothesized that the perceived complexity in implementation, already overburdened physical infrastructure, and high cost of treatment would delay adoption leading to additional stress on the clinical community advocating for access to treatment on behalf of patients. I was specifically interested in understanding how a commercial and investigational product came to be adopted at different sites over the same period of time and what other site-specific factors were at play. To test this hypothesis, we undertook a historical review to identify salient events and processes in the adoption of CAR T. A document analysis was performed using a historical approach to acquire data, which was used to construct a timeline of events comprising the innovation adoption process. Documents were acquired from published and grey literature, as well as AHS. Relevant emails were also obtained from a subset of participants. Through interviews, timeline data were supplemented where necessary and validated, then partitioned according to the stages in Roger's theory of Diffusion in an organization. We also aggregated stakeholders involved and

presented them as a network, providing an initial survey of parties active within the ecosystem, which is broadly generalizable to other health systems that wish to adopt innovations developed and manufactured in a grassroots fashion.

Major events affecting the adoption and implementation of both tisagenlecleucel and ACT-C01 included clinical meetings, mixed stakeholder meetings, and activities related to the business case and its review. The clinical sites (Cross Cancer Institute/University of Alberta Hospital; Tom Baker Cancer Centre/Foothills Medical Centre) undertook institutional preparations individually (with informal knowledge transfer between sites) and these were not a significant contributor to time from adoption to launch in relation to other processes. The most time-consuming processes in Calgary were related to the business case, and in Edmonton were related to legal challenges, regulatory review and manufacturing process development. The NABMT was able to secure FACT accreditation for their HSCT program through the process, get access to CAR T therapy for patients to prepare for IEC accreditation, as well as build new relationships with a potential partner for cell processing in the future. ABMT continued to grow its apheresis/CTL infrastructure and human resources through the business case and is well poised to continue its leadership in the field. Concurrent, salient events that impacted the process at both sites were the COVID-19 pandemic and the rollout of a new clinical information system across the province.

In addition to validating timeline data, to better illuminate the challenges to and facilitators of adoption encountered by stakeholders, semi-structured interviews were conducted. Fourteen of these were conducted remotely in the third quarter of 2021.. Key contributors were the past and present directors of each clinical centre's HSCT program, a hospital medical director, two high level AHS directors, a clinician scientist, and industry representatives. Data were analyzed using qualitative methods and coded inductively for challenges/facilitators, and grouped into sub-themes and themes. Two researchers independently reviewed the codes for internal and external validity. After inductive coding, the data was deductively analyzed using the Consolidated Framework for Implementation Research (CFIR) to evaluate its suitability in this novel setting and present the interview using a standardized approach.

Participants reported C/F across all five domains of the framework; of which, the inner setting, innovation characteristics and adoption process. The strength of the clinical evidence on CAR T preceding implementation was also a major enabler, allowing champions and implementation leaders to expedite the process and garner support, as was the existence of HSCT programs at each site. The perceived adoption cost and the process of acquiring additional clinical funding was a major challenge; it delayed the process, multiplied the stakeholders involved and yielded an insufficient product (as reported by frontline clinicians). Once payers negotiated the price at the provincial level, product cost was not a significant C/F.

The clinical staff on the frontlines of care were optimistic, then excited, becoming anxious and finally frustrated while waiting for access to the innovation. These individuals were major enablers of the process, especially when supported by partnerships with the private sector, philanthropic organizations, and universities. Administration and clinicians reflecting on the process noted they were glad that adoption took a bicentric approach and were optimistic about the future benefits of the innovation as well Alberta's position in the ecosystem. Second-hand information from patients treated with ACT-C01 relayed by nursing were positive. These accounts highlighted the gratitude of patients for being enrolled on trial and having access close to home. They also remarked that the process was smooth and well-coordinated and that the entire process was easier to tolerate than an autologous transplant.

Autologous cell therapy requires close coordination between commercial manufacturers and hospitals, leading to a conservative approach to rolling out the technologies and clinical trials after market approval. Pharma played a major role in the determination of where and when access to therapy became available, leading to access delays for patients in Alberta (where CAR T wasn't initially launched) compared to Quebec and Ontario. Clinician champions emerged to address the issue, and with support from ACF, U of A, and industry, were able to re-structure the innovation with existing manufacturing infrastructure and develop a further refined, point-of-care solution. This is a poignant example of how publicly funded healthcare in a collaborative ecosystem can work to develop local, cost-effective solutions tailored to patients. Additional research into the comparative effectiveness of the technologies is a fascinating avenue for future research.

Decentralized, point-of-care CAR T in Alberta offers benefits to patients, clinicians, and payers; however, several barriers exist. We identified two in particular: dated federal regulations and the resultant high costs of commercialization. With new evidence into the safety of lentivirally transduced CTPs and closed system bioreactors, regulators are now free to lower the standards for point-of-care produced cell products, as the EMA has already done. This is especially true for FACT accredited clinical laboratories, which have already safely manipulated patient-derived cell therapy products for years. Progressive regulation would remove another barrier to the reacquisition of control over manufacturing to the benefit of clinicians and payers, while providing a source of revenue for academic-clinical partnerships. It would be prudent for semi-autonomous hospital clinical research units to make a formal commitment to providing any clinical or research costs of locally developed innovations in-kind, reducing the burden on academic or clinician-researcher led projects.

Comparing the institutional C/F observed in this study to those in the literature[7–14], we see concordance between our results and those presented elsewhere. The most widely expressed sentiment among participants was that the clinical sites were constrained physically and financially. We saw both positive and negative results from this issue; new funding was acquired, and new stakeholders connected. More importantly however, frontline human resources were needlessly depleted, and patient access to medication was limited. This study has shown that the infrastructure, funding and human resources are available in this province to develop sustainable and transformative therapies; it is now the responsibility of government, health system administration and hospitals to nurture these innovations and proactively manage our valuable human resources and realize the potential of the next generation of technologies-- so they are ready to go when we need them.

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