

**Fecal microbiota transplantation in patients undergoing chimeric antigen receptor T-cell therapy and allogeneic stem cell transplant (ORCHID): A pilot study**

**Protocol Number:** FMT-CARTSCT

**Ozmosis Protocol Number:** OZUHN-038

**Protocol Version and Date:** v 1.0 17-Dec-2025

**Phase of Study:** Pilot study

**Sponsor:**

Abi Vijenthira, MD, SM, FRCPC  
Princess Margaret Cancer Centre  
700 University Avenue, OPG 6-707  
Toronto, Ontario M5G 1X6  
Tel: 416-946-4501 ext. 3377  
Fax: 416-946-4563  
E-mail: [abi.vijenthira@uhn.ca](mailto:abi.vijenthira@uhn.ca)

**Co-Principal Investigators:**

Abi Vijenthira, MD, SM, FRCPC  
Arjun Law, MD, FRCPC  
Susy Hota, MD, MSc, FRCPC  
Susan Poutanen, MD, MPH, FRCPC  
Bryan Coburn, MD, PhD, FRCPC

**Collaborators and other study personnel:**

Tiana Korbachech, MD, PhD  
Erinn McCarthy, BSc  
Terry Johnston, patient partner

**Investigational agent:** Fecal microbiota transplant (FMT)

**Clinical Trial Management Company:**

Ozmosis Research Inc.  
700 University Avenue  
Suite 217-2N, Toronto, ON M5G 1Z5  
Main Line: 416-634-8300  
Fax: 416-634-8333

**Protocol History**

Version 1.0, dated 17-Dec-2025

## PROTOCOL APPROVAL PAGE

**Protocol Number:** FMT-CARTSCT

**Version:** 1.0

**Version Date:** Dec 17, 2025

I have reviewed the protocol.

I agree to conduct the study as detailed in the protocol and in compliance with International Council for Harmonisation (ICH) Guidelines E6 (r2): Guideline for Good Clinical Practice (GCP) and all the ethical and regulatory considerations stated.

---

Dr. Abi Vijenthira

---

Date

## STUDY SYNOPSIS

<b>Study Title:</b>	Fecal microbiota transplantation in patients undergoing chimeric antigen receptor T-cell therapy and allogeneic stem cell transplant: A pilot study
<b>Study Sites:</b>	Princess Margaret Cancer Centre (single site study)
<b>Study Design:</b>	This is a single centre, non-randomized, single-arm interventional pilot study examining fecal microbiota transplantation in patients undergoing CAR-T or allogeneic stem cell transplantation (alloSCT)
<b>Duration:</b>	Approximately 2.5 years, including 2 years of recruitment, minimum 1 series of FMT treatments and a minimum 6 months of follow-up
<b>Planned Total Sample Size:</b>	20 eligible patients will be enrolled in this study – 10 patients with B-cell lymphoma undergoing CAR-T and 10 patients with AML/MDS undergoing alloSCT
<b>Investigational Agent:</b>	Fecal microbiota transplant (FMT)
<b>Study Objectives:</b>	<p><b>Primary Objective</b></p> <ul style="list-style-type: none"> <li>To evaluate the feasibility and safety of fecal microbiota transplantation (FMT) in patients undergoing CAR-T or allogeneic stem cell transplantation</li> </ul> <p><b>Secondary Objectives</b></p> <ul style="list-style-type: none"> <li>In patients undergoing CAR-T: To evaluate the incidence of all grade and Grade <math>\geq 3</math> cytokine release syndrome (CRS), and all grade and Grade <math>\geq 3</math> immune effector cell-associated neurotoxicity syndrome (ICANS)</li> <li>In patients undergoing alloSCT: To evaluate the incidence of all grade and Grade <math>\geq 3</math> acute graft-versus-host disease (GVHD) including gut GVHD</li> <li>To assess one and three month overall response rates after infusion of CAR-T cells or stem cells (alloSCT)</li> <li>To assess progression-free survival at 6 months</li> <li>To assess overall survival at 6 months</li> </ul> <p><b>Exploratory Objectives</b></p> <ul style="list-style-type: none"> <li>To evaluate baseline and day +30, +90, +180 T-cell phenotypic and functional subsets</li> </ul>

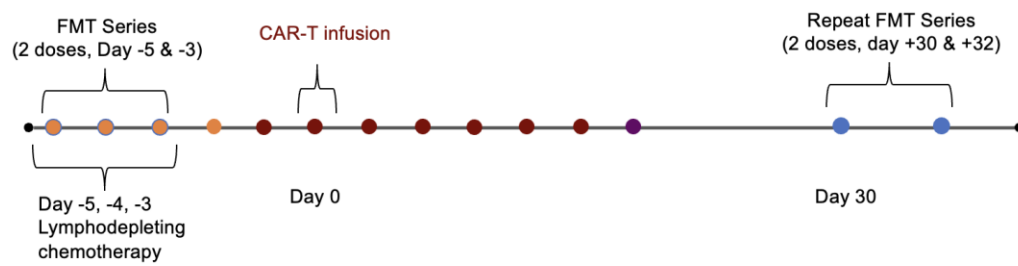
	<ul style="list-style-type: none"> <li>• To evaluate baseline and day +30, +90 intestinal microbiome diversity</li> <li>• To evaluate engraftment (Donor and recipient intestinal microbiome similarity)</li> <li>• To evaluate baseline and day +30, +90 plasma and urine bacterial metabolomics</li> <li>• To evaluate baseline and day +30, +90 incidence of antimicrobial resistant organism (ARO) (MRSA, VRE, ESBL, CBE) intestinal colonization by rectal swab</li> <li>• To evaluate incidence of bacteremia, urinary tract infections and/or <i>C. difficile</i> infection by day +30</li> <li>• To understand patient perspectives on FMT gathered by survey at baseline and on day +90</li> </ul>
<b>Inclusion/Exclusion Criteria:</b>	<p>Inclusion criteria (in brief):</p> <ol style="list-style-type: none"> <li>1. Men and women <math>\geq 18</math> years of age</li> <li>2. Diagnosis of the following: <ol style="list-style-type: none"> <li>a. B-cell lymphoma eligible for standard or care CAR-T therapy, or</li> <li>b. Patients with AML or high risk MDS with indication to undergo reduced-intensity conditioning alloSCT and an available matched related, unrelated, or haploidentical donor</li> </ol> </li> <li>3. ECOG 0-1</li> <li>4. Adequate bone marrow function defined as a neutrophil count <math>\geq 1.0 \times 10^9</math> L, HGB <math>\geq 80</math> g/L, and PLT count <math>\geq 20 \times 10^9</math> L</li> <li>5. Willing and able to participate in all required evaluations and procedures in this study.</li> <li>6. Ability to understand and the willingness to sign a written informed consent.</li> </ol> <p>See section 3.1 for a full list of inclusion criteria.</p> <p>Exclusion criteria (in brief):</p> <ol style="list-style-type: none"> <li>1. For patients undergoing alloSCT: plan to undergo myeloablative conditioning</li> <li>2. Use of investigational agents within the last 4 weeks before enrollment.</li> <li>3. Active or uncontrolled infection</li> <li>4. Autoimmune disorder currently being treated with disease-modifying therapy or with <math>\geq 10</math>mg/day</li> </ol>

	<p>prednisone</p> <ol style="list-style-type: none"> <li>5. Inflammatory bowel disease</li> <li>6. History of intestinal perforation</li> <li>7. Recent gastrointestinal surgical procedure within the past 4 weeks</li> <li>8. Pregnant or breast-feeding patients</li> <li>9. HIV infection with CD4 count &lt;200 or detectable viral load</li> <li>10. Serologic status reflecting active hepatitis B or C infection as follows: <ol style="list-style-type: none"> <li>a. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) with detectable hepatitis B virus (HBV) DNA. (Note, patients with undetectable HBV DNA are permitted to enroll if they are on Hepatitis B suppressive therapy)</li> <li>b. Patients with presence of hepatitis C virus (HCV) antibody and HCV RNA detectable</li> </ol> </li> <li>11. History of infection with antibiotic resistant organism in the last two years before enrollment (including ESBL, MRSA, VISA, VRSA, VRE, CPE)</li> <li>12. Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in the study</li> </ol> <p>See section 3.1 for a full list of exclusion criteria.</p>
<b>Screening Assessments:</b>	<ul style="list-style-type: none"> <li>• Informed consent</li> <li>• Medical history</li> <li>• Review of standard of care blood tests including HIV, Hepatitis B and C testing</li> <li>• Blood and urine collection for correlative studies</li> <li>• Stool Sample</li> <li>• Rectal Swab</li> <li>• Physical Exam</li> <li>• Participant questionnaire on perceptions and acceptability of FMT</li> <li>• Pregnancy Test</li> <li>• Disease Response B-cell Lymphoma, MDS, &amp; AML</li> </ul>
<b>Treatment and Post-Treatment Assessments:</b>	<ul style="list-style-type: none"> <li>• FMT series occurring prior to cellular therapy and 30 days after cellular therapy treatment</li> <li>• Post-treatment assessments will occur at Day +30, Day +90, and Day +180 after cellular therapy treatment</li> </ul>

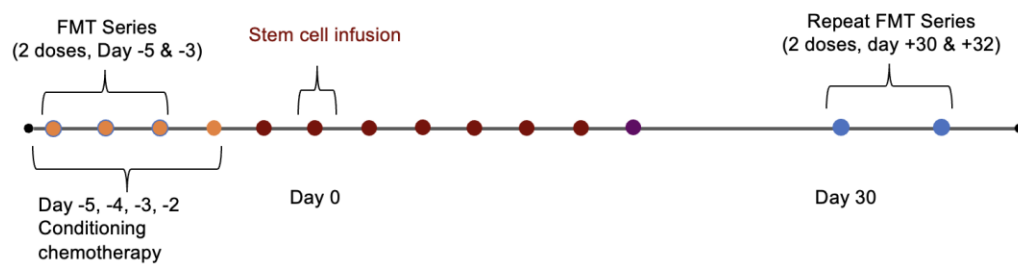
<b>Response:</b>	Standard of care disease response assessment per institutional guidelines
<b>Safety Variables &amp; Analysis:</b>	<p>Adverse Events unrelated to infection, CRS, ICANS, and GVHD be assessed as per CTCAE version 5.0. Infections will be assessed as per Bone Marrow Transplant Clinical Trials Network criteria. CRS and ICANS will be assessed as per ASTCT criteria. GVHD will be assessed per the Mount Sinai Acute GvHD International Consortium (MAGIC) criteria.</p> <p>See Section 7 for further details.</p>
<b>Statistical Analysis:</b>	See Statistical Considerations section for details

## TREATMENT SCHEMA

### CAR-T therapy protocol



### Allogeneic stem cell transplant protocol



## TABLE OF CONTENTS

1. BACKGROUND & RATIONALE.....	13
1.1 Background.....	13
1.2 Investigational Product .....	14
2. OBJECTIVES AND ENDPOINTS .....	17
2.1 Primary Objective .....	17
2.2 Secondary Objectives.....	17
2.3 Exploratory Objectives .....	18
3. PATIENT SELECTION .....	20
3.1 Eligibility criteria.....	20
4. STUDY PROCEDURES .....	23
4.1 Description of Procedures.....	23
4.2 Safety Monitoring .....	26
5. STUDY INTERVENTION .....	28
5.1 FMT Preparation.....	28
5.2 FMT Administration .....	30
5.3 General Guidelines for Concomitant Medications and Supportive Care .....	31
5.4 Duration of Therapy.....	31
5.5 Duration of Follow-Up .....	31
5.6 Subject Withdrawal/Discontinuation Criteria .....	32
5.7 Drug Dispensing and Accountability .....	32
6. DOSING DELAYS/DOSE MODIFICATIONS.....	33
7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS .....	34
7.1 List of Adverse Events and Reporting Requirements .....	34
7.2 Adverse Event Characteristics .....	34
7.3 Adverse events grading: Events not related to infection, CRS, ICANS, or GVHD: .....	36
7.4 Adverse events grading: Infectious events.....	37
7.5 Adverse events grading: CRS, ICANS, and GVHD .....	43
7.6 Serious Adverse Event Reporting .....	45
7.7 Abnormal Laboratory Value Reporting.....	47
7.8 Documentation of Adverse Events.....	47
7.9 Follow-Up of AEs, AESIs and SAEs .....	47
7.10 Deaths .....	48
7.11 Pregnancy.....	48
8. CORRELATIVE STUDIES.....	49
8.1 Ecological outcomes .....	49
8.2 Metabolomic studies .....	49
8.3 Immunologic studies.....	49
9. STUDY CALENDAR.....	50
DATA REPORTING / REGULATORY REQUIREMENTS .....	52
9.1 Compliance with Trial Registration and Results Posting Requirements.....	52
9.2 Patient Protection.....	52
9.3 Data Collection and Reporting.....	52
9.4 Subject Confidentiality and Access to Source Data/Documents .....	52
9.5 Study Monitoring/Auditing.....	53
9.6 Study Monitoring/Auditing.....	53
9.7 Quality Control and Quality Assurance .....	53
9.8 Data Management Guidelines .....	54

9.9	REB Composition .....	54
9.10	Initial Approval .....	54
9.11	Annual Re-Approvals .....	54
9.12	Amendments / Revisions .....	54
9.13	REB Refusals .....	54
9.14	Serious Adverse Events, Safety Updates, and Investigator Brochure Updates .....	54
9.15	Informed Consent Document .....	55
9.16	Consent Process/ Patient Eligibility .....	55
9.17	Site and Study Closure .....	55
10.	STATISTICAL CONSIDERATIONS .....	56
10.1	Study Design/Endpoints .....	56
	The primary endpoints are feasibility and safety. ....	56
10.2	Sample size/Accrual Rate .....	56
10.3	Secondary Endpoints .....	56
10.4	Exploratory Endpoints .....	56
10.5	Missing Data Handling .....	57
11.	DOCUMENTATION, RECORD ACCESS AND MAINTENANCE OF STUDY RECORDS ...	58
11.1	Documentation of Patient's Participation .....	58
11.2	Regulatory Requirements .....	58
11.3	Patient Confidentiality and Access to Source Data/Documents .....	58
11.4	Confidentiality of the Study .....	59
11.5	Study Data at the End of Registration of Clinical Trial .....	59
11.6	Data Reporting .....	59
11.7	Maintenance of Study Records .....	59
12.	ADMINISTRATIVE PROCEDURES .....	60
12.1	Amendments to the Protocol .....	60
12.2	Protocol Deviations and Violations .....	60
12.3	Premature Discontinuation of the Study .....	60
13.	LEGAL ASPECTS .....	61
13.1	Publication Policies and Disclosure of Data .....	61

## **Abbreviations**

AE: Adverse effects

AlloSCT: Allogeneic stem cell transplant

ALT: Alanine Aminotransferase

ARO: Antibiotic resistant organisms

AST: Aspartate Aminotransferase

ASTCT: American Society for Transplantation and Cellular Therapy

BA: Bile acids

BiPAP: Bilevel positive airway pressure

BMI: Body mass index

BSA: Body surface area

CAR-T: Chimeric antigen receptor T-cell

CBE: Carbapenemase-resistant *Enterococci*

CMV: Cytomegalovirus

CNS: Central nervous system

CPAP: Continuous positive airway pressure

CPO: Carbapenemase-producing Organisms

CRS: Cytokine release syndrome

CTCAE: Common Terminology Criteria for Adverse Events

DLT: Dose-limiting toxicity

EBV: Epstein barr virus

ESBL: Extended-spectrum beta-lactamases

FMT: Fecal microbiota transplantation

GI: Gastrointestinal

GU: Genitourinary

GVHD: Graft-versus-host-disease

HCW: Health care workers

HHV-6: Human herpes virus-6

HIV: Human immunodeficiency virus

HOMA-IR: Homeostatic Model Assessment for Insulin Resistance

HSV: Herpes simplex virus

HTLV: Human T-lymphotrophic virus

ICANS: Immune effector cell-associated neurotoxicity syndrome

ICMJE: Committee of Medical Journal Editors

IV: Intravenous

MRSA: Methicillin resistant *Staphylococcus aureus*

MTOP: Microbiota Therapeutics Outcomes Program

NPO: Nil per os; Nothing by mouth

NOS: Not otherwise specified

ORR: Overall response rate

OS: Overall survival

PCR: Polymerase chain reaction

PFS: Progression-free survival

PTLD: Post-transplant lymphoproliferative disorder

RIC: Reduced-intensity conditioning

SCFA: Short-chain fatty acids

SMC: Safety monitoring committee

VISA: Vancomycin-intermediate *Staphylococcus aureus*

VRE: Vancomycin-resistant *Enterococci*

VRSA: Vancomycin-resistant *Staphylococcus aureus*

VZV: Varicella zoster virus

WOCBP: Women of Childbearing Potential

## 1. BACKGROUND & RATIONALE

### 1.1 Background

In patients with relapsed or refractory B-cell lymphoma, a standard of care therapeutic option to achieve long term remission is CD19 chimeric antigen receptor T-cell (CAR-T) therapy. This is a unique concept involving engineering patients' autologous T-cells to target the CD19 antigen on lymphoma cells; however a minority of patients achieve long term remission.<sup>1-6</sup> At the same time, patients undergo risks with this treatment, including cytokine storm (cytokine release syndrome, CRS) and neurologic toxicity (immune effector cell-associated neurotoxicity syndrome, ICANS).<sup>7</sup> Though the outcomes of CAR-T are promising, there is room to improve upon the efficacy and toxicity of this therapy.

Similarly, in patients with moderate to high-risk acute myeloid leukemia or myelodysplastic syndrome, allogeneic stem cell transplant (alloSCT) represents a potential cure for their disease. There is long-established efficacy in utilizing donor derived stem cells to create a new hematopoietic system, and donor T-cells to cause a graft-versus-tumour effect to eliminate microscopic persistence of disease. However, as a by-product, 30% of patients develop moderate-to-severe (Grade 2 to 4) graft-versus host-disease (GVHD), with 10% of patients having severe disease.<sup>8</sup> Additionally, long term survival is less than 50% in all-comers and less than 30% in patients who develop severe GVHD.<sup>8</sup> Thus, there is also room to improve upon the efficacy and safety of alloSCT.

An emerging area of therapeutic interest is the intestinal microbiome, which has been shown to be associated with responses to cancer therapeutics including chemotherapy,<sup>9</sup> immune checkpoint blockade,<sup>10-14</sup> and cellular therapies,<sup>15-18</sup> potentially by impacting host anti-tumour immune response.

Microbiome studies in patients undergoing CAR-T therapy have found impaired alpha diversity compared to healthy controls.<sup>16</sup> Broad antibiotic exposure within 3 weeks prior to CAR-T has been associated with significantly decreased progression-free survival (PFS) which was confirmed in an independent cohort, with the highest hazard ratio associated with broad spectrum antibiotics.<sup>18</sup> However, even when excluding such patients, species, pathway, and gene variance still contributed significantly to treatment response and disease progression. Higher abundance of taxa such as *Ruminococcus*, *Bacteroides*, *Faecalibacterium*, *Akkermansia*, and *Bifidobacterium* have correlated with higher rates of complete response and improved progression-free survival (PFS),<sup>16-18</sup> while peptidoglycan biosynthesis or D- galactose biosynthesis pathways have associated with early disease progression and worse survival at 6 months.<sup>18</sup> Certain microbes have also been associated with higher rates of neurotoxicity.

The contribution of the microbiome has also been well established in patients undergoing alloSCT, where a higher diversity of microbiota were associated with a lower risk of death in international independent cohorts, including death attributable to GVHD.<sup>15</sup> Patients have impaired microbiome diversity compared to healthy controls at baseline, while during the transplant, a characteristic pattern of domination by single taxa occurs, supporting the use of pre-transplant and post-transplant normalization of intestinal microbiota.<sup>15</sup>

## 1.2 Investigational Product

### 1.2.1 Background on fecal microbiota transplantation (FMT)

The concept of FMT is the replacement of abnormal gut microbiome in the recipient with the microbiome of a healthy donor who has been screened for infectious diseases, health conditions that may be associated with dysbiosis, and risk behaviours that could increase the risk of acquiring infectious diseases. FMT is an established therapy in the management of recurrent *C. difficile* infection.<sup>19</sup> The therapeutic use of FMT has been studied in numerous malignancies including hematological cancers.<sup>20</sup>

### 1.2.2 Background on route of administration of FMT

Notably, there is no standard for processing and administering human-to-human FMT.<sup>21</sup> The donor stool is typically homogenized and filtered and either administered directly or frozen for later use.<sup>21-23</sup> Gastrointestinal tubes, colonoscopy, enema, and recently even oral capsules are used to administer FMT.<sup>21</sup>

To date, many studies have been published showing the efficacy of FMT to treat *C. difficile* colitis. The mode of administration does not seem to have a major impact on the efficacy.<sup>24</sup> (See Investigator Brochure). The principal investigator group has previously used enema for treatment of *C. difficile* infection (Clinicaltrials.gov (NCT01226992); CTA File #: 9424-U0288/2-25C, Control #: 124081). Enema will be used for FMT administration in the current study.

### 1.2.3 Prior data on safety

FMT is generally considered a safe procedure. There are common minor adverse effects including transient diarrhea, abdominal cramps or pain, bloating, flatulence, and constipation. Risk of infection transmission has been a concern in the past, with prior reports of extended-spectrum beta-lactamase (ESBL)-producing *E. coli* infection and Shiga toxin-producing *E. coli* infection associated with deaths, possibly transmitted via the FMT product.<sup>25</sup> This led to more stringent testing of stool, with a recent registry study suggesting a 4% risk of infection by 6 months.<sup>26</sup> Other theoretical risks include intestinal perforation from enema or colonoscopic administration, and unknown long-term impacts on other aspects of health.

FMT has been performed on immunocompromised individuals including those undergoing allogeneic stem cell transplant. A challenge with immunocompromised individuals is determining whether bacteremia/sepsis events are related to the FMT product or are related to patients' underlying disease and treatment. The largest study was a Phase II 2:1 randomized study of FMT versus placebo in 100 patients with acute myeloid leukemia or undergoing alloSCT who received oral FMT a median of 43 days after chemotherapy or 23 days after SCT, respectively.<sup>27</sup> The primary objective was to reduce the incidence of infections compared to placebo. This randomized trial was able to establish the safety of FMT in this population. No grade 3 or higher adverse events occurred within 24 hours of product administration. Only one grade 3 or higher gastrointestinal adverse event (diarrhea) occurred within 7 days after FMT. A blood stream infection with cytomegalovirus viremia (CMV) occurred within 7 days after FMT and was the only event that counted toward the stopping rule in the study. The patient was CMV-

seropositive and their HCT and FMT donors were both CMV-seronegative, making a relationship with FMT unlikely.

Another Phase study II reported on an oral FMT product in patients undergoing alloSCT with severe GVHD. The publication included 24 patients in the trial and 52 patients in an extended access program.<sup>28</sup> In the trial population, five infectious complications, including 3 episodes of sepsis, could not be excluded from being related to the study intervention, though none of the strains involved in the sepsis episodes were found in the donor product. In the extended access program, 18 pharmacovigilance cases were reported among 52 treated patients, including 11 cases of bacteremia/sepsis. Overall, the product was concluded to be safe in this report.

Multiple other prospective studies comprising between 7 and 80 patients of patients receiving FMT who were undergoing alloSCT and/or had acute GVHD illustrated the safety of this product in this population, with mainly minor or transient AEs such as abdominal distention, cramps, or nausea, resolving within hours.<sup>27,29-34</sup> One study reported two episodes of bacteremia which were from organisms either found in the host at baseline, or not found in the product;<sup>34</sup> another pilot study reported one case of bacteremia, it was not stated whether this was related to the FMT product;<sup>30</sup> a final study noted pseudomonas bacteremia in a patient with a persistent pseudomonas skin infection.<sup>29</sup>

Overall, the breadth of the data including a large randomized study suggest that FMT appears safe in an immunocompromised population of patients with hematologic malignancies.

#### 1.2.4 Prior data on efficacy

The study by Rashidi et al described showed that FMT ameliorated intestinal dysbiosis and was safe, but it did not achieve its primary objective of reducing infections.<sup>27</sup> Other case reports and small prospective studies prior to alloSCT have also shown that FMT can restore gut dysbiosis and decolonize antibiotic resistant organisms (AROs) in patients with multi-drug resistant bacteria.<sup>35-37</sup> Furthermore, prospective studies and case reports have shown that FMT can be a salvage treatment for severe gut GVHD.<sup>28,31-34,38-41</sup>

There is also an ongoing study of FMT in the proposed study population. NCT04935684 is a Phase II randomized study evaluating FMT by enema route in 150 patients undergoing alloSCT within 4 weeks of engraftment, with a primary outcome of occurrence of GVHD and engraftment.<sup>42</sup>

#### 1.2.5 Rationale

Despite the novel clinical findings described, no published study has shown a potential therapeutic role for pre-emptively restoring normal intestinal microbiota prior to the cellular therapy infusion in unselected patients undergoing these procedures. Specifically, all published studies in alloSCT have used FMT after engraftment, or as a salvage treatment for gut GVHD. Additionally, no therapeutic study of FMT has been conducted on patients undergoing CAR-T therapy.

Our hypothesis is that we will be able to establish the feasibility and safety of FMT transfer in these populations, and explore endpoints of improved treatment toxicity, efficacy, and immunological, metabolomic, and ecological outcomes.

#### 1.2.6 Study design

This is a single centre open-label, single arm pilot clinical trial of 20 patients, including 10 patients undergoing CAR-T therapy for relapsed/refractory B-cell lymphoma, and 10 patients undergoing alloSCT for AML or MDS. This trial will be conducted in compliance with the protocol, GCP and Health Canada regulations.

As this is a pilot study with primary endpoints of feasibility and safety, we will exclude patients with a history of infection or colonization with AROs within the last 2 years prior to enrollment. Given that all patients at Princess Margaret Cancer Centre undergoing alloSCT for malignant conditions receive cyclophosphamide for GVHD prophylaxis which increases the risk of bloodstream infections,<sup>43</sup> we will only include patients receiving reduced-intensity conditioning (rather than myeloablative conditioning) to mitigate this risk.<sup>43</sup>

## 2. OBJECTIVES AND ENDPOINTS

### 2.1 Primary Objective

Objective	Endpoints
To evaluate the feasibility and safety of FMT in patients undergoing CAR-T or allogeneic stem cell transplantation	<p>Feasibility: Ability to recruit the target population, retention, and successful administration of the intervention</p> <p>Safety: In each cohort, occurrence of serious adverse events or adverse events of special interest (AESIs) Grade <math>\geq 3</math> that are judged by the investigator as possibly, probably, or definitely related to the FMT intervention</p>

### 2.2 Secondary Objectives

Objective	Endpoints
In patients undergoing CAR-T: To evaluate the incidence of all grade and Grade $\geq 3$ CRS, and all grade and Grade $\geq 3$ ICANS	Incidence of all grade CRS, grade $\geq 3$ CRS, all grade ICANS, grade $\geq 3$ ICANS
In patients undergoing alloSCT: To evaluate the incidence of all grade and Grade $\geq 3$ acute GVHD including gut GVHD	Incidence of all grade and grade $\geq 3$ acute GVHD after allogeneic stem cell transplant
To assess one and three month overall response rates after infusion of CAR-T cells or stem cells (alloSCT)	<p>ORR determined by investigator assessment:</p> <p>-For patients with lymphoma, those with confirmed complete response or partial response by Lugano criteria on PET scan</p> <p>-For patients with MDS, achieving complete remission, partial remission, or hematologic independence based on peripheral blood and bone marrow assessment</p> <p>-For patients with AML, achieving complete remission, partial remission, or a morphologic leukemia free state based on peripheral blood and bone marrow assessment</p>

To assess progression-free survival at 6 months	PFS determined by investigator assessment defined as the time from the date of infusion of cellular therapy to (first) disease recurrence documented via radiologic, laboratory, and/or clinical assessment, or death, or last follow up when alive without disease recurrence/progression
To assess overall survival at 6 months	OS, defined as the time from the date of infusion of cellular therapy to the date of death from any cause

## 2.3 Exploratory Objectives

Objective	Endpoints
To evaluate baseline and day +30, +90, +180 T-cell phenotypic and functional subsets	Phenotypic and functional T-cell subsets, including but not limited to, CD3, CD4, CD8 T-cell subsets, T-cell phenotypic and functional markers by flow cytometry, T-cell functional assays such as interferon gamma release assay
To evaluate baseline and day +30, +90 intestinal microbiome diversity	Alpha diversity (Shannon diversity, species richness, Berger-Parker dominance); MET-2 species relative abundance by shotgun metagenomic sequencing; Pseudomonadota, Enterobacteriaceae, Staphylococcus, Enterococcus, Pseudomonas, and Candida species relative abundance; Obligate anaerobe richness and cumulative relative abundance; Butyrogenic anaerobe richness and cumulative relative abundance; Compositional dissimilarity (Bray-Curtis dissimilarity) between groups and within groups and individuals/between timepoints; Absolute bacterial abundance (by 16S gene qPCR); Log-fold changes in relative abundance between baseline and post-treatment samples will be determined and 'engraftment' for any species defined as >1-log increase.
To evaluate engraftment (Donor and recipient intestinal microbiome similarity)	Compositional dissimilarity/similarity (beta-diversity) will be assessed between groups and sample pairs (i.e. pre/post intervention or donor/recipient) using Bray-Curtis compositional dissimilarity; whole blood flow cytometry for anti-FMT bacterial antibodies as a correlate of engraftment and immunogenicity

To evaluate baseline and day +30, +90 plasma and urine bacterial metabolomics	Plasma, and urine SCFA and 1°BA/2°BA concentrations
To evaluate baseline and day +30, +90 incidence of antimicrobial-resistant organisms (MRSA, VRE, ESBL, CBE) intestinal colonization by rectal swab	Incidence of MRSA, VRE, ESBL, and CBE colonization by rectal swab
To evaluate incidence of bacteremia, urinary tract infections and/or <i>C. difficile</i> infection by day +30	Incidence of bacteremia, urinary tract infections, and <i>C. difficile</i> infection by Day +30
To understand patient perspectives on FMT gathered by survey at baseline and on day +90	Patient perspectives on FMT gathered by survey, comparing quantitative responses at baseline and day +90, and describing qualitative responses

### 3. PATIENT SELECTION

#### 3.1 Eligibility criteria

Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study. Waivers will not be granted for this study.

##### 3.1.1 Inclusion criteria

For inclusion in the study patients must fulfill all of the following criteria:

1. Men and women  $\geq 18$  years of age
2. Diagnosis of the following:
  - a. Indolent or aggressive B-cell lymphoma eligible for standard or care CAR-T therapy (Cohort A), or
  - b. Patients with AML or high risk MDS with indication to undergo reduced-intensity conditioning alloSCT, with an available matched related, unrelated, or haploidentical donor (Cohort B)
3. ECOG 0-1
4. Adequate marrow function defined by:
  - a. Hemoglobin  $\geq 80$  g/L without transfusion dependence within the last 7 days
  - b. Platelet count  $\geq 20 \times 10^9$ /L without transfusion dependence within the last 7 days
  - c. Neutrophil count  $\geq 1.0 \times 10^9$ /L without growth factor support within the last 7 days
5. Adequate liver function as indicated by aspartate aminotransferase (AST) and alanine aminotransferase (ALT)  $\leq 2.5 \times$  the institutional upper limits of normal (ULNs) value; serum total bilirubin  $\leq 1.5 \times$  ULN (unless documented Gilbert's syndrome)
6. Adequate renal function as defined as creatinine clearance  $\geq 30$  mL/min directly measured with a 24-hour urine collection or calculated according to the modified formula of Cockcroft-Gault equation or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) calculation
7. Life expectancy  $> 6$  months
8. Women of childbearing potential (WOCBP) who are sexually active must use highly effective methods of contraception during treatment and up to 6 months after the last dose of protocol therapy. Men who are sexually active must use highly effective methods of contraception during treatment and up to 6 months after the last dose of protocol therapy. Men require an agreement to remain abstinent (ie, refrain from heterosexual intercourse) or use a condom, and an agreement to refrain from donating sperm. Periodic abstinence and withdrawal are not acceptable methods of contraception. Fertility preservation options should be discussed. Examples of highly effective contraceptive methods include an agreement to remain abstinent (ie, refrain from heterosexual intercourse), bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
9. Willing and able to participate in all required evaluations and procedures in this study.
10. Ability to understand and the willingness to sign a written informed consent.

### 3.1.2 Exclusion criteria

Subjects will be ineligible for this study if they meet any of the following criteria:

1. For patients undergoing alloSCT (Cohort B): plan to undergo myeloablative conditioning
2. Use of investigational agents within the last 4 weeks before enrollment.
3. Active or uncontrolled infection
4. Autoimmune disorder currently being treated with disease-modifying therapy or with  $\geq 10$ mg/day prednisone
5. Inflammatory bowel disease
6. History of intestinal perforation
7. Gastrointestinal surgical procedure within the past 4 weeks before enrollment
8. Pregnant or breast-feeding patients
9. HIV infection with detectable viral load or CD4 count  $< 200$
10. Serologic status reflecting active hepatitis B or C infection as follows:
  - a. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) with detectable hepatitis B virus (HBV) DNA. (Note, patients with undetectable HBV DNA are permitted to enroll if they are on Hepatitis B suppressive therapy)
  - b. Patients with presence of hepatitis C virus (HCV) antibody and HCV RNA detectable
11. History of infection or known colonization with antibiotic resistant organism in the last two years before enrollment (including ESBL, MRSA, VISA, VRSA, VRE, CPE)
12. Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in the study

### 3.1.3 Enrollment Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. Studies or procedures that are performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained as long as they are within protocol defined windows. The informed consent process is to be fully documented and the prospective participant must receive a copy of the signed informed consent document. Screening procedures are listed in Section 4.

All patients will be screened by the principal investigator or sub-investigators prior to entry into this study. An explanation of the study and discussion of the expected side effects and full disclosure of the "informed consent document will take place. Eligible and consented patients will be registered into the study.

After the subject has signed and dated the Informed Consent Form (ICF), all screening procedures have been completed, and eligibility has been confirmed, the subject can be enrolled into the study.

Registration will be done through Ozmosis Research Inc. Sites will assign each patient with a patient ID number which should be used on all documentation and correspondence.

Prior to registering a patient, each institution must have submitted all necessary regulatory documentation to Ozmosis Research Inc. Access to the eCRFs will only be granted once this has been received.

No patient can receive protocol treatment until eligibility has been confirmed and the Patient Enrollment Form has been submitted to Ozmosis Research Inc. All eligibility criteria must be met at the time of enrollment. Waivers will not be accepted. Any questions should be addressed with Ozmosis Research Inc. prior to enrollment.

Sites will fax in the signed, completed Patient Enrollment Form to Ozmosis Research Inc. at 416-634-8333, or e-mail to [ozmclinical@ozmosisresearch.ca](mailto:ozmclinical@ozmosisresearch.ca). The CTS/CTM will then review the registration form for completion. There will be NO confirmation of registration sent to the site. Patients are considered to be registered once the Patient Enrollment Form has been successfully delivered to Ozmosis. Only after this has been done, can the patient receive study treatment.

Protocol treatment should begin within 7 working days of patient enrollment.

All eligible patients registered into the study will be entered into a patient registration log at Ozmosis Research Inc.

The following information will be required at the time of registration:

- Patient ID trial code
- Treatment centre and investigator
- Patient's partial date of birth

Note: it is the responsibility of the investigator in charge to satisfy him or herself that the patient is indeed eligible before registering.

The Patient Enrollment Form must be completed, and signed by the investigator prior to enrollment. There are 2 sections to the Patient Enrollment Form:

- SCREENING (top section): this section is completed by the site and should be faxed to 416-634-8333, or e-mailed to [ozmclinical@ozmosisresearch.ca](mailto:ozmclinical@ozmosisresearch.ca) at the time of screening.
- ENROLLMENT (bottom section): this section is completed by the site at the time of patient enrollment. The site will fax the signed and completed Patient Enrollment Form to Ozmosis Research Inc. at 416-634-8333, or e-mailed to [ozmclinical@ozmosisresearch.ca](mailto:ozmclinical@ozmosisresearch.ca).

## 4. STUDY PROCEDURES

For a summary of study procedures, see STUDY CALENDAR

The Study Calendar summarizes the trial procedures to be performed at each visit. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Furthermore, additional evaluations/testing may be deemed necessary for reasons related to subject safety.

### 4.1 Description of Procedures

#### 4.1.1 Study treatment overview

Eligible patients will be identified during routine standard of care waitlist meetings for patients undergoing CAR-T or alloSCT therapy. Patients cleared to undergo CAR-T or alloSCT procedures routinely attend in-person follow up visits at the study site. During such standard of care visits, patients will be approached by the study coordinator for informed consent. It is anticipated that this visit will be the pre-apheresis clearance visit for patients undergoing CAR-T therapy, and the pre-alloSCT clearance visit in which a donor has been identified for the patient, and patients are medically cleared.

If patients provide informed consent and meet study eligibility guidelines, they will be enrolled into the study.

Initial FMT series (see section 5.2 for further details): Patients will receive their initial FMT series with two doses separated by 48 hours during their lymphodepleting chemotherapy (for patients receiving CAR-T, day -5 and day -3) or conditioning chemotherapy (for patients receiving alloSCT, day -5 and day -3). These dates were selected as infusion dates to ensure that the FMT administration occurs prior to the onset of chemotherapy-induced neutropenia. Patients must have an ANC  $\geq 1.0 \times 10^9/L$  documented within 7 days prior to the FMT administration.

For patients receiving CAR-T therapy, the lymphodepleting chemotherapy regimens are aligned with standard of care and may vary based on physician preference and institutional practice.

- YESCARTA (axicabtagene ciloleucel): Prior to cell therapy infusion date (Day 0), Day -5 to Day -3: cyclophosphamide 500 mg/m<sup>2</sup> and fludarabine 30 mg/m<sup>2</sup> IV daily
- TECARTUS (brexucabtagene autoleucel): Prior to cell therapy infusion date (Day 0), Day -5 to Day -3: cyclophosphamide 500 mg/m<sup>2</sup> and fludarabine 30 mg/m<sup>2</sup> IV daily
- KYMRIA (tisagenlecleucel): Prior to cell therapy infusion date (Day 0), Day -5 to Day -3: cyclophosphamide 250 mg/m<sup>2</sup> and fludarabine 25 mg/m<sup>2</sup> IV daily
- BREYANZI (lisocabtagene maraleucel): Prior to cell therapy infusion date (Day 0), Day -5 to Day -3: cyclophosphamide 300 mg/m<sup>2</sup> and fludarabine 30 mg/m<sup>2</sup> IV daily

For patients receiving alloSCT, the conditioning chemotherapy regimens are aligned with standard of care and the regimen selected may vary based on physician preference and institutional practice:

- RUH-FB2: Prior to cell therapy infusion date (Day 0), fludarabine 35mg/m<sup>2</sup> IV daily on

- Day -5 to Day -2, busulfan 3.2mg/kg IV daily on Day -5 and Day -4
- RUH-FB2T(200): Prior to cell therapy infusion date (Day 0), fludarabine 35mg/m<sup>2</sup> IV daily on Day -5 to Day -2, busulfan 3.2mg/kg IV daily on Day -5 and Day -4, total body irradiation 200 cGy on Day -1
- RU-FluTreo42: Prior to cell therapy infusion date (Day 0), fludarabine 35mg/m<sup>2</sup> IV daily on Day -5 to Day -2, treosulfan 14g/kg IV daily on Day -5 to Day -3
- RU-FluTreo30: Prior to cell therapy infusion date (Day 0), fludarabine 35mg/m<sup>2</sup> IV daily on Day -5 to Day -2, treosulfan 10g/kg IV daily on Day -5 to Day -3

Additionally, patients should not have any signs, symptoms, or diagnosis of active infection at the time of FMT administration. Prior to administering their initial series, patients will provide a fecal swab and bloodwork to bank as a regulatory precaution in case of safety concerns with their FMT product.

Second FMT series (see section 5.2 for further details): A second FMT series is due at Day +30. The second FMT series will only be administered if patients have a neutrophil count of  $ANC \geq 1.0 \times 10^9/L$  without growth factor support for a 7 day period, documented within 7 days prior to the FMT administration. Additionally, patients should not have any signs, symptoms, or diagnosis of active infection at the time of FMT administration. If patients remain reliant on growth factors and/or they have concerns of active infection, the second FMT series will be delayed by a maximum of 30 days, after which time it will be omitted. Prior to the second series, in addition to study procedures, patients will provide a fecal swab and bloodwork to bank as a regulatory precaution in case of safety concerns with their FMT product.

Follow-up: At Day +90 and +180, patients will be seen during their routine post-cellular therapy follow up visit for study visits. Further details of study procedures during these visits are in the Study Calendar.

#### 4.1.2 Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial. Informed consent of study procedures may be obtained prior to the 60-day screening window

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the Research Ethics Board (REB)'s approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form

or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to REB requirements, applicable laws and regulations and Sponsor requirements.

#### 4.1.3 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

#### 4.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee, including history of severe and/or anaphylactic food allergies. Medical history will include all active conditions, and any condition previously diagnosed that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

#### 4.1.5 Prior and Concomitant Medications Review

##### 4.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

##### 4.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable Serious Adverse Events (SAEs) should be recorded as defined in Section 7.6.

##### 4.1.5.3 Permitted Concomitant Medication

Permitted concomitant medication include:

- Highly effective contraceptive methods including hormonal contraceptives that inhibit ovulation, hormone releasing intrauterine devices, and copper intrauterine devices must be used by WOCBP who are sexually active during treatment and up to 6 months after the last dose of protocol therapy.
- Pico-Salax as required in the study

##### 4.1.5.4 Prohibited Concomitant Medications

Prohibited concomitant medications include:

- Any investigational agents other than those under investigation in this study.

- Any disease modifying therapy or administration of  $\geq 10$  mg/day prednisone for treatment of autoimmune disorder.

#### 4.1.6 Disease Details and Treatments

##### 4.1.6.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

##### 4.1.6.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

##### 4.1.7 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment.

##### 4.1.8 Participant questionnaires

Participants will fill out a baseline questionnaire regarding their perceptions of FMT. At Day +90, they will fill out a second questionnaire regarding their experience and perceptions of FMT.

#### 4.2 Safety Monitoring

Given the immunocompromised nature of patients on this study, only 10 patients will be initially accrued and the initial safety will be assessed by a safety monitoring committee (SMC). The committee will be composed of clinical specialists with experience in oncology and infectious diseases and who have no direct relationship with the study. They will be charged with overseeing the monitoring of safety of participants in the clinical trial, and the conduct, progress, validity, and the integrity of the data. The committee will review all relevant data to assess tolerability to approve further subjects to be enrolled thereafter.

The SMC will meet at any point deemed necessary during the study on its own initiative or at the request of the sponsor and in particular to analyze safety data. Any unexpected safety event including SAEs and AESIs Grade  $\geq 3$  that are possibly, probably, or definitely related to the FMT will be reported to the SMC, and will require that the study be placed on a hold while the SMC review the safety event.

The meetings will take place between the participating site investigators, the Sponsor and Ozmosis Research to review patient safety after 10 patients complete their series of FMT administrations and at least 7 days of follow up after the second administration of the last patient have passed. During the initial review period or at any time during the study there are two or more SAE or AESI considered possibly, probably, or definitely related to the FMT intervention in either cohort, enrollment to that cohort will close.

An “Accrual Hold Notice” will be sent out to Sponsor and site personnel by Ozmosis Research Inc. once the study has recruited the necessary patients.

Within 7 working days of each patient completing their second FMT series, the following sections of the eCRF and source documentation for laboratory results, must be completed:

- Study Treatment Data
- Adverse Events
- Laboratory Results

Additional information may also be requested by Ozmosis Research Inc. from the study site. It is imperative that the eCRF pages listed above are completed within 7 working days after the last patient has completed Day +34, as the information will be used to assess safety.

If a patient fails to complete the safety observation period (e.g. shows disease progression or stops treatment for reasons other than a safety concern), additional patients may be added to ensure a minimum of 10 patients. The SMC may recommend enrolling further patients to facilitate collection of additional safety data. The decision to enroll additional patients will be made in consultation with the SMC.

The SMC will be responsible for reviewing the following activities: participant accrual, summary of all adverse events captured via routine and expedited reporting; a summary of deviations; any response information; monitoring reports, and summary comments provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request. A review of outcome results (response, toxicity and adverse events) and factors external to the study (such as scientific or therapeutic developments) will also be discussed.

## 5. STUDY INTERVENTION

If the patient qualifies, based on the Screening evaluations, he/she will be enrolled according to the procedures outlined below.

### 5.1 FMT Preparation

#### 5.1.1 FMT Donors

Stool samples for this study will be obtained via donations through the Microbiota Therapeutics Outcomes Program (MTOP) at the University Health Network and Sinai Health in Toronto, Ontario. Donors will be evaluated according to MTOP guidelines, Health Canada Regulations and standard institutional practices. Individual donations will be used to manufacture FMT.

#### 5.1.2 Identification and Screening of FMT Donors

FMT donors will be supplied from MTOP, using existing criteria and standard procedures for identification and screening (see Investigator Brochure). In short, healthy, adult potential donors (PDs) are recruited through advertisements in the downtown Toronto region and the MTOP website. PDs undergo screening for eligibility through self-screening questionnaire, telephone pre-screening, medical assessment, mental health questionnaires and blood testing for diabetes risk (homeostatic model assessment for insulin resistance – HOMA-IR). They subsequently undergo serologic, urine, rectal swab, upper respiratory tract and/or oral specimen and stool testing for infectious diseases and antibiotic-resistant organism colonization. Approved donors (who pass all of the aforementioned screening) provide repeat stool donations (goal 3-5 times per week).

Bookend testing of stool for AROs (MRSA, VRE, ESBL and CPO), common enteric pathogens, *SARS-CoV-2* and mpox occurs at minimum two-month intervals. Rescreening for blood borne pathogens and sexually-transmitted infections occurs at least every 6 months. FMT donations provided up to 2 weeks preceding re-screening are released only if re-screening is negative for AROs and all other screened infectious diseases. In addition, while donating stool to MTOP, FMT donors complete self-screening questionnaires with every donation for ongoing assessment of their medical health, intake of common allergens, and risk of acquiring infectious diseases. If a risk for infection is determined to be present on the questionnaire (e.g. travel to an endemic area for infectious disease), the donor is placed in a washout period prior to being rescreened to re-enter the program. Diabetes risk (HOMA-IR score), anthropometric measurements and mental health questionnaires are repeated at least every 12 months. For patients who have a history of severe and/or anaphylactic food allergies, the donor FMT is screened to ensure there has been no recent intake of any of the listed allergens.

FMT donations are processed, concentrated and frozen at -80C, until requested for FMT. Donor feces are collected at home and are delivered to MTOP within 24-48 hours. Frozen FMT is stored up to 5 years without losing significant viability, as per MTOP internal verification of FMT storage conditions.<sup>44</sup> MTOP protocols follow Health Canada guidance for FMT donor

screening and selection<sup>45</sup> and are approved by the UHN Research Ethics Board (CAPCR ID: 16-5404).

### 5.1.3 FMT Manufacturing

FMT manufacturing will follow modified methodologies, based on a previous randomized controlled trial from the MTOP program.<sup>46</sup>

#### *Fresh Donor Stools FMT:*

- a. For the 50g/filtrate dose, fifty (50) grams of screened donor feces will be weighed and homogenized with 300 mL of sterile 0.9 N NaCl using a sterile 330 micron micro-filter-separated double-compartment polyethylene bag in the Stomacher® Lab Blender. . For the 100g/filtrate dose, one hundred (100) grams of screened donor feces will be weighed and homogenized with 300 mL of sterile 0.9 N NaCl using a sterile 330 micron micro-filter-separated double-compartment polyethylene bag in the Stomacher® Lab Blender.
- b. The sample will be homogenized using the Stomacher® Paddle Blender for 30 seconds at 300rpm until it is a milk-shake consistency.
- c. The resulting fecal filtrate will be transferred to an enema bag constituting a single “FMT dose”.
- d. Part of the final fecal filtrate will be stored in the –80°C freezer in the event that further testing is required in the future.
- e. All aliquots of fecal filtrate will be labeled with a unique donor identification number.
- f. Any reusable equipment will be autoclaved in order to eliminate *C. difficile* spores. The Stomacher® will be cleaned as specified by the manufacturers before and after each use including the use of a sporicidal agent. The preparation area will be cleaned with a sporicidal agent before and after each use.

#### *Preparation of Frozen FMT Concentrate:*

- a. Fifty (50) grams of screened donor feces will be weighed and homogenized with 45 mL of sterile 0.9 N NaCl + 5 ml glycerol (to make 10% final concentration glycerol) using a sterile 330 micron micro-filter- separated double-compartment polyethylene bag in the Stomacher® Paddle Blender.
- b. The sample will be homogenized using the Stomacher® Paddle Blender for 30 seconds at 300rpm until it is a milk-shake consistency.
- c. The resulting fecal filtrate will be transferred to a 50 mL Falcon tube with screw top and frozen at -80 °C.
- d. Part of the final fecal filtrate will be stored in the –80°C freezer in the event that further testing is required in the future.
- e. All aliquots of fecal filtrate will be labeled with a unique donor identification number.

- f. Any reusable equipment will be autoclaved in order to eliminate *C. difficile* spores. The Stomacher® will be cleaned as specified by the manufacturers before and after each use including the use of a sporicidal agent.
- g. The preparation area will be cleaned with a sporicidal agent before and after each use.

These activities will be carried out within a designated biosafety cabinet in the UHN-SHS Clinical Microbiology Laboratory.

#### 5.1.4 Thawing, Dilution and Packaging of frozen FMT:

Frozen FMT will be thawed at room temperature over 2.5 hours in order to best maintain the integrity of microorganisms.

For enema administration, of the 50g/filtrate dose of FMT, one (1) Falcon tube of thawed FMT concentrate will be diluted to a final volume of 300 ml and transferred to an enema bag.

For enema administration of 100g/filtrate dose of FMT, two (2) Falcon tube of thawed FMT concentrate will be diluted to a final volume of 300 ml and transferred to an enema bag.

#### 5.1.5 Transportation of FMT product

Enema bags and screw top containers containing prepared fecal filtrate will be transported at room temperature to the FMT procedure room in a biosafety specimen transportation bag following Transportation of Dangerous Goods procedures.

### 5.2 FMT Administration

FMT will be administered by enema. Two hours prior to the procedure, patients will be advised to refrain from consuming any food or drink, a practice known as being ‘nil per os’ alternatively nothing by mouth (NPO). Medications may be taken using sips of water. Patients may eat a regular diet but will be advised to use a bowel preparation instructions using Pico-Salax the night before the FMT procedure will be given. If the bowel preparation is incomplete, missed, or the patient refuses bowel prep, they may still proceed with the FMT procedure.

Rectal infusion of FMT will be administered every 48 hours for 2 doses, on 2 separate occasions, detailed in the study calendar. For each series of FMT administrations, the first dose will be 100g and the second will be 50g. Each FMT will be delivered using a single dose (300 ml of prepared fecal filtrate containing 100g or 50g of stool from a donor) delivered using an enema bag and rectal catheter. The procedure, including preparation steps, will take less than 20 - 30 minutes. Patients will be asked to lie down retaining the enema product for 20 minutes, changing position (left lateral decubitus, supine, right lateral decubitus, supine) every 5 minutes. Patients will be observed for 30 minutes post-FMT administration for immediate adverse events. Patients will have a mandatory rectal swab and serum collection prior to the first FMT of each treatment series which will be banked and recalled in the event that there is a concern for transmission of infectious agents from FMT. These are performed for quality of care purposes.

FMT by enema will be administered by a physician or nurse practitioner with training in enema administration of FMT. For patients undergoing CAR-T therapy, the first FMT series will typically occur in the Autologous Day Hospital when they attend their standard of care visits for leukapheresis chemotherapy. For patients undergoing alloSCT as an outpatient, the first FMT series will typically occur in the Allogeneic Day Hospital (outpatient alloSCT), or in the inpatient unit (inpatient alloSCT), during their standard of care conditioning chemotherapy. Patients must have an ANC  $\geq 1.0 \times 10^9/L$  documented within 7 days prior to the FMT administration. These dates were selected as infusion dates to ensure that the FMT administration occurs prior to the onset of chemotherapy-induced neutropenia. Additionally, patients should not have any signs, symptoms, or diagnosis of active infection at the time of FMT administration.

The second FMT administration will occur in either the inpatient or outpatient setting depending on whether the patient has been discharged from hospital by the time their second FMT series is due at Day +30. The second FMT series will only occur if patients have a neutrophil count of  $ANC \geq 1.0 \times 10^9/L$  without growth factor support for the last 7 days, documented within 7 days prior to the FMT administration. Additionally, patients should not have any signs, symptoms, or diagnosis of active infection at the time of FMT administration. If patients remain reliant on growth factors or there are concerns of infection, the second FMT series will be delayed by a maximum of 30 days, after which time it will be omitted.

### 5.3 General Guidelines for Concomitant Medications and Supportive Care

#### 5.3.1 Concomitant Medications

Concomitant medications to control side effects of therapy will be given at the discretion of the investigator. Medications that are considered necessary for the subject's welfare, and which are not expected to interfere with the evaluation of the study procedure, may be given at the discretion of the Investigator.

### 5.4 Duration of Therapy

Safety/efficacy assessments will be made from enrollment onto trial through 180 days after cellular therapy which is considered the active treatment phase of the protocol.

Subjects will continue on this phase and defined observation/tests will be repeated until one of the following criteria applies:

1. Disease progression.
2. Clinical progression.
3. Termination of the protocol by a regulatory agency or Sponsor, or study medication can no longer be provided.
4. Significant non-compliance with the protocol schedule in the opinion of the investigator.
5. Intercurrent illness that prevents further study participation.
6. Serious safety event that is judged to be possibly, probably or definitely related to the study intervention by the investigator
7. The Subject decides to withdraw from the study.
8. General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.

### 5.5 Duration of Follow-Up

Patients will be followed on protocol until 180 days after cellular therapy to collect information on safety assessment and disease response.

### 5.6 Subject Withdrawal/Discontinuation Criteria

Patients are free to withdraw from the study at any time. If a patient withdraws consent, they will be asked if they are withdrawing consent to:

- All further participation in the study including any further follow up
- Withdrawal of the use of any samples

A patient who withdraws consent will be asked about the reason(s) for withdrawal and the presence of any AE. The investigator will promptly notify the Sponsor and will make every effort to complete the End of Study assessments. All withdrawn subjects with ongoing clinically significant clinical or laboratory findings will be followed until the finding is resolved or medically stable; reasonable attempts will be made to follow-up with subjects.

A patient may also be discontinued from the study if, in the investigator's judgment, continued participation would pose unacceptable risk to the subject or to the integrity of the study data. All procedures for discontinuation must be completed. Reasons for discontinuation may include:

- Noncompliance with the study
- Unacceptable toxicity
- Disease progression
- Continuation in the study is not in the best interest of the patient as judged by the investigator
- Protocol deviation or violation
- Study terminated by sponsor

### 5.7 Drug Dispensing and Accountability

The UHN-SHS Clinical Microbiology Laboratory will be responsible for the receipt, storage, dispensing and tracking of the investigational drug. The lab personal will prepare the correct dosage of study agent to be administered to the study participant. The responsibility for drug accountability, including monitoring of drug dispensed to each study participant, drug supply reconciliation, record maintenance and documentation of drug destruction due to expiry or remaining supply at the end of the clinical trial, will be the responsibility of the participating clinical site. The local Pharmacist or delegate will maintain an accurate record of the receipt of investigational drug supply and the dispensing of investigational drug to each study participant including the quantity, batch or lot number, date of dispensing and any unused drug.

At study close-out, expired investigational drug should be destroyed at high temperature incineration or by the standard institutional practice. Documentation of destruction is required to be completed by each clinical site.

## 6. DOSING DELAYS/DOSE MODIFICATIONS

There are no dose modifications applicable to this protocol as the study treatments include standard dose FMT. As stated, patients must have an ANC  $\geq 1.0 \times 10^9/\text{L}$  documented within 7 days prior to the first FMT administration, and they must have an ANC  $\geq 1.0 \times 10^9/\text{L}$  without growth factor support within the last 7 days, documented within 7 days prior to the second FMT administration. Additionally, patients should not have any signs, symptoms, or diagnosis of active infection at the time of FMT administration. If these criteria are not met at time of first FMT, patients would not meet study eligibility criteria. If these criteria are not met at the time of the second FMT series, it can be delayed for up to 30 days after which time it will be omitted.

If an adverse event occurs after enrollment that prevents a particular subject from receiving the study treatment but then resolves, the subject can be rescreened for study treatment if considered appropriate by the study investigator. The subject must, however, continue to meet eligibility for treatment. In cases where the FMT product does not meet manufacture specification criteria for administration, the subject will be withdrawn from the study.

## 7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

### 7.1 List of Adverse Events and Reporting Requirements

This study will utilize the CTCAE version 5.0 for toxicity and Adverse Event reporting, for adverse events other than those related to infection, CRS, ICANS, and GVHD. For adverse events related to infection, the Bone Marrow Transplant Clinical Trials Network Guidance will be used.<sup>47</sup> For adverse events related to CRS and ICANS, the American Society for Transplantation and Cellular Therapy (ASTCT) 2019 guidance will be used.<sup>48</sup> For adverse events related to GVHD, the Mount Sinai Acute GvHD International Consortium (MAGIC) criteria will be used.<sup>49</sup>

Please refer to sections 7.3, 7.4 and 7.5 for detailed information on adverse events grading as above.

#### 7.1.1 Expected Adverse Events and Protocol-Specific Expedited Adverse Event

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs and the characteristics of an observed AE will determine whether the event requires expedited reporting as an SAE in addition to routine reporting. In addition, hospitalizations for routine procedures, protocol treatment, blood sampling, investigations and tissue biopsies are NOT considered SAE in this protocol.

##### 7.1.1.1 Expected Adverse Events for FMT

Expected adverse events include minor adverse effects such as transient diarrhea, abdominal cramps or pain, bloating, flatulence, and constipation. Adverse events of special interest (AESI) include Grade  $\geq 3$  bowel perforation, bacteremia and/or sepsis, or ICU admission events occurring within 48 hours of each FMT administration. These events, and any serious adverse event will be subjected to expedited reporting.

### 7.2 Adverse Event Characteristics

The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. The term disease progression should not be reported as an AE or SAE, however, medically significant individual events and/or laboratory abnormalities associated with disease progression (see definition of disease progression below) that fulfill the AE or SAE definition should be reported. An abnormal laboratory finding (including ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a

laboratory abnormality, the diagnosis or medical condition should be reported (e.g. renal failure, hematuria) not the laboratory abnormality (e.g. elevated creatinine, urine red blood cell increased).

AEs may be treatment emergent (i.e. occurring after initial receipt of investigational product) or non-treatment emergent. A non-treatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product. Non-treatment-emergent AEs occurring prior to study treatment and not related to study procedures will be captured as baseline symptoms.

Effective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or non-serious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

- CTCAE term (AE description) and Grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE) Version 5.0. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP web site [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)
- Attribution of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

**Associated with the use of the drug:**

There is a reasonable possibility that the experience may have been caused by the drug/biologic.

**Life threatening adverse drug experience:**

Any adverse drug/biologic experience that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred.

**Serious adverse event:**

Any event is an AE occurring at any dose that results in any of the following outcomes:

- Death.
- A life-threatening AE (The patient was, in the view of the Investigator, at immediate risk of death from the event as it occurred. It does not mean that the event, had it occurred in a more severe form, might have caused death).
- Hospitalization or prolongation of existing hospitalization (complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other

serious criteria, the event is serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered to be an AE).

- A persistent or significant disability/incapacity (A substantial disruption of a subject's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, accidental trauma (i.e., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption).
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization or the development of drug dependency or drug abuse).

**Events not considered to be serious adverse events are:**

- hospitalizations for the routine treatment or monitoring of the studied indication, not associated with any deterioration in condition,
- treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen,
- admission to a hospital or other institution for general care, not associated with any deterioration in condition, or
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Any SAE occurring after the patient has provided informed consent for the main research study and until 90 days after date of cellular therapy must be reported.

Unexpected adverse drug experience: Any adverse drug experience, the nature, frequency, or severity of which is not consistent with the investigator brochure, or not consistent with the risk information described above as a protocol-specific expected adverse event (see "Expected Adverse Events and Protocol-Specific Expedited Adverse Event Reporting Exclusions," above).

**7.3 Adverse events grading: Events not related to infection, CRS, ICANS, or GVHD:**

For adverse events not related to infection, CRS, ICANS, or GVHD, definitions found in the CTCAE version 5.0 will be used for grading the severity (intensity) of AEs. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures

- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject’s usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

#### 7.4 Adverse events grading: Infectious events

For infectious adverse events, as noted in guidance from the Bone Marrow Transplant Clinical Trials Network,<sup>47</sup> it is recognized the CTCAE grading system does not adequately capture the nuances of infections in the context of transplant and cell therapy trials, where patients have multifactorial immunodeficiency and unique susceptibilities to infections.<sup>47</sup> CTCAE's distinction in grading based on parenteral versus oral therapies does not accurately reflect disease severity in patients who are electively hospitalized for their cell therapy. These patients may also have mucositis or GVHD. In these contexts patients may receive medications intravenously for reasons unrelated to the severity of their infection.

This trial therefore uses the BMT CTN Guidance for grading infectious complications, as a more precise measure to capture the morbidity and mortality associated with infections.

Table 1. Severity Grading Table for Bacterial Infections

Type of infection/severity grade	Grade 1	Grade 2	Grade 3
Bacterial infections	Bacteremia with skin flora [eg, coagulase-negative <i>Staphylococcus</i> (CoNS), <i>S. epidermidis</i> ), <i>Corynebacterium</i> , or <i>Cutibacterium</i> ( <i>Propionibacterium</i> )] requiring antibiotics for ≤14 days of therapy for treatment	Bacteremia due to other organisms (not skin flora)	Bacteremia with deep organ involvement (for example, new or worsening pulmonary infiltrates, endocarditis, brain abscess) Septic Shock with Bacteremia Endocarditis Brain abscess or Meningitis Active tuberculosis infection
	Bacterial focus NOS requiring systemic antibiotics for ≤14 days of therapy for treatment (for example, urinary tract infection) Bacterial focus NOS requiring only topical, ocular, or otic treatments	Bacterial focus NOS with persistent signs/symptoms or persistent positive cultures requiring antibiotics for >14 days of therapy (GI, GU, abdominal)	

Type of infection/severity grade	Grade 1	Grade 2	Grade 3
		infections, myositis)	
	Cellulitis responding to initial therapy within 14 days	Cellulitis requiring a change in therapy due to progression or systemic treatment for >14 days Localized or diffuse skin and soft tissue infections requiring incision with or without drain placement but no debridement	Fasciitis or other skin and soft tissue infection requiring surgical debridement
	Any bacterial pneumonia not requiring supplemental oxygen	Any bacterial pneumonia requiring low-flow oxygen*	Bacterial pneumonia requiring high-flow oxygen† or positive-pressure ventilation‡
	<i>C. difficile</i> toxin- or PCR-positive stool with diarrhea <1L / day (<5 episodes / day) without abdominal pain (child <20 mL/kg/day)	<i>C. difficile</i> toxin- or PCR-positive stool with diarrhea ≥1 L / day (≥5 episodes/day) (child ≥20 mL/kg/day) or with abdominal pain	<i>C. difficile</i> toxin or PCR-positive stool with ileus, colon dilation, toxic megacolon, or need for surgical intervention

\*Low flow defined as oxygen by nasal cannula ≤ 6L/minute.

†High-flow oxygen defined as oxygen by nasal cannula at >6L/minute.

‡Continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), intubation with mechanical ventilation.

CNS: Central nervous system; GI: gastrointestinal; GU: genitourinary; NOS: not otherwise specified; PCR: polymerase chain reaction

Table 2. Severity Grading Table for Fungal Infections

Type of infection/severity grade	Grade 1	Grade 2	Grade 3
Fungal infections	Mucocutaneous candidiasis (excluding esophagitis), including oral thrush and vaginal candidiasis Dermatophyte infections (tinea)	<i>Candida</i> esophagitis diagnosed by endoscopy	Fungemia including candidemia
		Fungal sinusitis confirmed radiologically without orbital, brain, or bone involvement.	Fungal sinusitis confirmed radiologically with orbital, brain, or bone involvement
		Fungal pneumonia or pulmonary nodules (unless requiring high-flow oxygen* or positive pressure ventilation†)	Fungal pneumonia or pulmonary nodules requiring high-flow oxygen or positive-pressure ventilation
		Fungal skin and soft tissue infection without fungemia, involvement of other sites, or need for debridement‡	Disseminated or deep-seated fungal infections (for example, CNS, visceral, or ocular fungal infections) or fungal infections requiring operative debridement or other surgery
		<i>Pneumocystis jirovecii</i> pneumonia (unless requiring high-flow oxygen or positive pressure ventilation)	<i>Pneumocystis jirovecii</i> pneumonia requiring high-flow oxygen or positive-pressure ventilation

\*High-flow oxygen defined as oxygen by nasal cannula at >6L/minute.

†Continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), intubation with mechanical ventilation.

‡This category is listed to capture locally invasive fungal infection that require treatment eg, IV related mucormycosis or skin and soft tissue involvement with endemic yeast etc.

CNS: Central nervous system

Table 3. Severity Grading Table for Viral Infections

Type of infection/severity grade	Grade 1	Grade 2	Grade 3
Viral infections	Mucosal (oral, esophageal, vaginal, penile) or cutaneous HSV infection requiring oral antiviral therapy or observation	Mucosal (oral, esophageal, vaginal, penile) or cutaneous HSV infection requiring IV nutrition due to pain associated with infection or IV antiviral therapy	HSV infection with end-organ involvement (encephalitis, hepatitis, pneumonitis)
	Dermatomal herpes zoster (shingles) affecting $\leq 2$ dermatomes	VZV infection involving 3 or more dermatomes	Severe VZV infection with end-organ involvement (encephalitis, hepatitis, pneumonitis, retinitis) or with organ dysfunction or severe sepsis (for example, coagulopathy)
	Asymptomatic CMV viremia not requiring treatment	CMV viremia requiring therapy or CMV viremia requiring a change in therapy due to resistant or refractory disease or persistent viremia beyond 4 wk while on treatment	CMV end-organ involvement (eg, lung, intestines, eye)
	EBV viremia not requiring treatment	EBV viremia requiring treatment	EBV PTLT
	Adenoviral infection not requiring treatment	Adenoviral upper respiratory infection, viremia, or symptomatic viruria requiring treatment	Adenovirus with end-organ involvement, including pneumonitis but excluding conjunctivitis and upper respiratory tract infections
	HHV-6 viremia not requiring treatment	HHV-6 infection with attributed symptoms or cytopenias requiring treatment	HHV-6 with end-organ involvement (such as encephalitis, hepatitis, pneumonitis)
	BK viremia or viruria with cystitis not requiring intervention except anti-spasmodic or pain medication	BK viremia or viruria with cystitis with clinical consequence requiring treatment, for example, continuous bladder irrigation, antiviral therapy, or procedural intervention	BK viremia or viruria with end-organ damage (for example, kidney injury)

Type of infection/severity grade	Grade 1	Grade 2	Grade 3
		Enterocolitis with enteric (GI) viruses	
	Symptomatic upper and lower tract respiratory virus (excludes adenovirus, but including SARS-CoV-2) not requiring supplemental oxygen	Viral pneumonia or pneumonitis (excludes adenovirus but includes SARS-CoV-2; see above) requiring low-flow oxygen	Lower tract respiratory viruses (including SARS-CoV-2) requiring high-flow oxygen or positive-pressure ventilation
	Viremia (virus not otherwise specified) not requiring therapy	Any viremia (virus not otherwise specified) requiring therapy	Any viral encephalitis, meningitis, or end-organ disease

CMV: cytomegalovirus; EBV: Epstein barr virus; GI: gastrointestinal HHV-6: human herpes virus-6; HSV: herpes simplex virus; PTLN: Post-transplant lymphoproliferative disorder; VZV: Varicella zoster virus

Table 4. Severity Grading Table for Parasitic Infections and Clinically Defined Infections

Type of infection/severity grade	Grade 1	Grade 2	Grade 3
Parasitic infections	Giardiasis or other parasitic gastrointestinal infection with diarrhea $\leq 1$ L / day (<5 episodes / day) (child $\leq 20$ mL/kg/day)	Giardiasis or other parasitic gastrointestinal infection with diarrhea $\geq 1$ L / day (5 episodes / day) (child $\geq 20$ mL/kg/day) or with abdominal pain	
	Chronic strongyloidiasis treated with oral ivermectin or other oral therapies		<i>Strongyloides</i> hyperinfection or disseminated infection
	Toxoplasma DNAemia without organ involvement resolving spontaneously (without treatment)	Toxoplasma DNAemia without organ involvement requiring treatment	CNS or another organ toxoplasmosis
Clinically defined infections	Pneumonia or bronchopneumonia not requiring supplemental oxygen	Pneumonia or bronchopneumonia requiring low-flow oxygen	Any acute pneumonia requiring high-flow oxygen or positive-pressure ventilation
	Fever with negative cultures responding to treatment within 14 days		
	Clinically documented infection not requiring inpatient management*	Sepsis without an identified organism (excluding patients receiving immune effector therapy diagnosed with cytokine release syndrome (CRS))	Septic shock without an identified organism (excluding patients receiving immune effector therapy diagnosed with CRS)
		Typhlitis without severe sepsis, ileus, or need for surgical intervention	

\*Patients should be reported as having CRS and graded as such, not infection, if they exhibit CRS symptoms or signs within the time frame expected for a given product AND the treating team prefers CRS over infection as the cause of the symptoms or signs.

## 7.5 Adverse events grading: CRS, ICANS, and GVHD

American Society for Transplantation and Cellular Therapy (ASTCT) 2019 will be used to grade CRS and ICANS AEs.<sup>48</sup>

Table 5. ASTCT CRS Grading

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature $\geq 38^{\circ}$ Celsius	Temperature $\geq 38^{\circ}$ Celsius	Temperature $\geq 38^{\circ}$ Celsius	Temperature $\geq 38^{\circ}$ Celsius
with				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
and/or <sup>1</sup>				
Hypoxia	None	Requiring low-flow nasal cannula <sup>2</sup> or blow-by	Requiring high-flow nasal cannula <sup>2</sup> , facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

\*Fever is defined as temperature  $38^{\circ}\text{C}$  not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

<sup>1</sup>CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of  $39.5^{\circ}\text{C}$ , hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

<sup>2</sup>Low-flow nasal cannula is defined as oxygen delivered at  $\leq 6$  L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at  $>6$  L/minute.

BiPAP: Bilevel positive airway pressure; CPAP: Continuous positive airway pressure

Table 6. ASTCT ICANS Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness <sup>1</sup>	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile

				stimuli to arouse. Stupor or coma.
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings <sup>2</sup>	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated intracerebral pressure/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging <sup>3</sup>	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICE: Immune effector cell encephalopathy

ICE Scoring: Orientation: orientation to year, month, city, hospital: 4 points; Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points; Following commands: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point; Writing: ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point; Attention: ability to count backwards from 100 by 10: 1 point

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

N/A indicates not applicable.

\*A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

<sup>1</sup>Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

<sup>2</sup>Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

<sup>3</sup>Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

## **GVHD Grading:**

The EBMT-NIH-CIBMTR Task Force recommendations supporting the use of the Mount Sinai Acute GvHD International Consortium (MAGIC) criteria<sup>49</sup> will be used to grade GVHD events.

Table 7. GVHD Grading

<b>Stage</b>	<b>Skin (active erythema only)</b>	<b>Liver (bilirubin)</b>	<b>Upper GI</b>	<b>Lower GI (stool output/day)</b>
<b>0</b>	No active (erythematous) GVHD rash	< 2 mg/dl (34.2 umol/L)	No or intermittent nausea, vomiting or anorexia	Adult: < 500 ml/day or <3 episodes/day Child: < 10 ml/kg/day or <4 episodes/day
<b>1</b>	Maculopapular rash <25% BSA	2–3 mg/dl (34.2-52.3 umol/L)	Persistent nausea, vomiting or anorexia	Adult: 500–999 ml/day or 3–4 episodes/day Child: 10–19.9 ml/kg/day or 4–6 episodes/day
<b>2</b>	Maculopapular rash 25 – 50% BSA	3.1–6 mg/dl (53.0-102.6 umol/L)	-	Adult: 1000–1500 ml/day or 5–7 episodes/day Child: 20 – 30 ml/kg/day or 7–10 episodes/day
<b>3</b>	Maculopapular rash > 50% BSA	6.1–15 mg/dl (104.3-256.5 umol/L)	-	Adult: >1500 ml/day or >7 episodes/day Child: > 30 ml/kg/day or >10 episodes/day
<b>4</b>	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation > 5% BSA	>15 mg/dl (>256.5 umol/L)	-	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume).

BSA: body surface area

Overall clinical grade (based upon most severe target organ involvement):

- Grade 0: No stage 1–4 of any organ
- Grade I: Stage 1–2 skin without liver, upper GI or lower GI involvement
- Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI
- Grade III: Stage 2–3 liver and/or stage 2–3 lower GI, with stage 0–3 skin and/or stage 0–1 upper GI
- Grade IV: Stage 4 skin, liver or lower GI involvement, with stage 0–1 upper GI

## **7.6 Serious Adverse Event Reporting**

### **7.6.1 Sponsor Notification**

Any serious adverse event, regardless of whether or not it is considered related to investigational product or study procedure(s), must be reported to Ozmosis Research Inc. within 24 hours of the Investigator, or other site personnel, learning of the event by a completed SAE form. The adverse event must be submitted through a completed SAE form and be completely described in the CRF. Whenever possible, SAEs should be reported by diagnosis term, not as a constellation of symptoms. All deaths should be reported with the primary cause of death as the AE term, as

death is typically the outcome of the event, not the event itself. If study procedure is discontinued because of an SAE, this information must be included in the SAE report.

#### AESI and SAE Reporting Instructions:

All AESIs and SAEs must be reported as follows:

Within 24 hours:                      Report initial information (on trial specific SAE report form) by fax or e-mail to:

Ozmosis Research Inc.  
Phone: 416-634-8300  
Fax: 416-634-8333  
E-mail: [ozmsafety@ozmosisresearch.ca](mailto:ozmsafety@ozmosisresearch.ca)

The initial information should always contain:

- Name of Reporter/Investigator,
- Subject Identification,
- Adverse Event Term,
- Study Drug Dose and Start/Stop Dates

On the next working day:      Fax or e-mail completed trial-specific Serious Adverse Event form

#### 7.6.2      Reporting Serious Adverse Events to Health Canada

Ozmosis Research Inc. will provide expedited reports of on-study SAEs to Health Canada for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

All adverse signs and symptoms which occur during or following the course of drug administration/investigational product infusion must be reported in detail on the subject's CRF. This description is to include the nature of the sign or symptom, time of onset in relation to drug application, duration, severity, and possible relationship to drug, required therapy, and outcome. The subject should be followed until the adverse reaction is resolved, or until in the opinion of the Principal Investigator, reversal of the reaction is not likely to occur.

#### 7.6.3      SAE Follow-up

Follow-up SAE report is subject to the same timelines as the initial report and is sent to the same parties to whom the original Serious Adverse Event Form was sent. A new SAE form is completed for the follow-up, stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication or progression of the original event should be reported as a follow-up to that event. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation.

#### 7.6.4 REB Notification of SAEs

Ozmosis Research Inc. will notify all Investigators of all SAEs that are reportable to regulatory authorities in Canada from this trial. This includes all serious events that are unexpected and related to protocol treatment. Investigators must notify their Research Ethics Boards (REBs) and file the report with their Investigator Site File. Documentation that SAEs have been reported to REBs must be kept on file at Ozmosis Research Inc. Documentation can be any of the following:

- letter from the REB acknowledging receipt
- stamp from the REB, signed and dated by REB chair, acknowledging receipt
- letter demonstrating the SAE was sent to the REB

All expedited SAEs occurring within a centre should also be reported to local REBs.

#### 7.7 Abnormal Laboratory Value Reporting

For abnormal laboratory values, it is the responsibility of the Principal Investigator or his designate to assess the clinical significance of each abnormality. Only abnormal laboratory values that can be assessed for Grade using CTCAE Version 5.0 will be documented. The Investigator will determine whether abnormal laboratory values are considered clinically significant and represent AEs based on their medical judgment.

Data on all adverse experiences/toxicities regardless of seriousness must be collected for documentation purposes only.

#### Clinical Laboratory Abnormalities:

All abnormal laboratory values should be captured on source documentation and assessed for clinical significance by the Investigator. Only abnormal laboratory values deemed clinically significant should be listed as AEs in the CRFs. All clinically significant abnormal laboratory results will be followed up until the related AE resolves, returns to  $\leq$  Grade 1 or baseline value in the follow-up period. Clinically significant laboratory abnormalities will be dictated in the clinic notes. Additionally, laboratory abnormalities resulting in an intervention are considered to be clinically significant.

#### 7.8 Documentation of Adverse Events

All AEs must be captured in the source documents, as well as reported in Medidata. AEs reported using SAE forms must also be reported in Medidata.

All serious and non-serious AEs occurring from the start of FMT administration until 180 days after cellular therapy must be recorded as AEs on the CRF. The Investigator should review all documentation (e.g., hospital progress notes, laboratory, or diagnostic reports) relative to the event being reported.

#### 7.9 Follow-Up of AEs, AESIs and SAEs

SAEs and AEs should be followed until 180 days after cellular therapy or until they are resolved (return to normal or baseline values), stabilized, improve to  $<$  Grade 2, or the subject is lost to

follow-up and cannot be contacted. Additional investigations (*e.g.*, laboratory tests, diagnostic procedures, or consultation with other healthcare professionals) may be required to completely investigate the nature and/or causality of an AE or SAE. If the patient dies during the study or within 7 following the last dose of the FMT, any postmortem findings (including histopathology) should be reported to Ozmosis Research Inc. CRF data should be updated with any new information as appropriate.

#### 7.10 Deaths

All deaths that occur during the study, including the protocol-defined follow-up period must be reported as follows:

Death which is clearly the result of disease progression, or a complication of disease progression should be reported at the next visit and documented in the eCRF but should **not** be reported as an SAE.

Where death is not due (or not clearly due) to disease progression, the AE causing the death must be reported as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of disease progression, if appropriate, and should assign main and contributory causes of death.

Deaths with an unknown cause should always be reported as an SAE. A post-mortem may be helpful in the assessment of the cause of death.

#### 7.11 Pregnancy

Any pregnancy of a study subject or of a study subject's partner that occurs during study participation should be reported for pregnancies that occur up to 30 days after the last FMT administration.

If pregnancy occurs, then the investigator or other site personnel should inform Ozmosis Research within 24 hours of when he/she becomes aware of it.

If the study subject is the father, then their partner will be provided with a pregnancy consent form to be reviewed and completed. To ensure patient safety each pregnancy must also be reported to the trials office. If the subject agrees, the pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

## 8. CORRELATIVE STUDIES

While the concepts of pharmacodynamics, pharmacokinetics and pharmacogenomics are established in pharmacology and routinely integrated into clinical trials, equivalent concepts have not been established for microbiome-targeting therapeutics. We will assess the following microbiome-informed biomarkers:

### 8.1 Ecological outcomes

1. Ecological outcomes will be assessed by 16S rRNA gene and shotgun metagenomic sequencing to assess:
  - a. Alpha diversity (Shannon diversity, species richness, Berger-Parker dominance);
  - b. MET-2 species relative abundance by shotgun metagenomic sequencing;
  - c. Pseudomonadota, Enterobacteriaceae, *Staphylococcus*, *Enterococcus*, *Pseudomonas*, and *Candida* species relative abundance;
  - d. Obligate anaerobe richness and cumulative relative abundance;
  - e. Butyrogenic anaerobe richness and cumulative relative abundance;
  - f. Compositional dissimilarity (Bray-Curtis dissimilarity) between groups and within groups and individuals/between timepoints;
  - g. Absolute bacterial abundance (by 16S gene qPCR).
  - h. Log-fold changes in relative abundance between baseline and post-treatment samples will be determined and 'engraftment' for any species defined as >1-log increase.
2. Engraftment:
  - a. Compositional dissimilarity/similarity (beta-diversity) will be assessed between groups and sample pairs (i.e. pre/post intervention or donor/recipient) using Bray-Curtis compositional dissimilarity.
  - b. Anti-Donor FMT antibodies will be assessed by a flow-cytometric assay to determine pre-treatment and post-treatment anti-FMT bacterial antibodies as a correlate of engraftment and immunogenicity.

### 8.2 Metabolomic studies

1. Metabolomic outcomes will be assessed by shotgun metagenomic sequencing and targeted gene detection to assess:
  - a. Antimicrobial gene richness, abundance and diversity;
  - b. Butyrate biosynthesis gene abundance (by qPCR);
  - c. *Plasma microbial metabolite concentrations* - SCFA and 1°BA/2°BA concentrations;

### 8.3 Immunologic studies

Immunological studies of T-cell phenotypic and functional subsets will be assessed by laboratory testing at baseline, Day +30, Day +90 and Day +180.

## 9. STUDY CALENDAR

The following schedule of assessments applies to all subjects. More frequent assessments should be obtained if clinically indicated.

Interaction number	1	2	3	4	5	6	7	8	9	10	11	12
Timeline (day, in relation to cell infusion)	Screening	-5	-3	-1	0	+1	+7	+30	+32	+34	+90	+180
Time window (days)	-60	+/- 1	+/- 1	+/- -1				-3/ +30	-3/ +30	-3/ +30	+/- 14	+/- 14
Informed consent <sup>9</sup>	x											
Inclusion and exclusion criteria	x											
Diagnosis	x											
Demographics (Age, Sex)	x											
Medical history baseline	x											
Physical exam including vital signs (blood pressure, heart rate, respiration rate oxygen saturation, temperature), ECOG, height and weight -Full physical exam at baseline -Symptom directed physical exam at D-5, D30 and D90	x	x						x			x	
Participant questionnaire on perceptions and acceptability of FMT		x									x	
FMT administration		x <sup>8</sup>	x					x <sup>2</sup>	x <sup>2</sup>			
Cell infusion (CAR-T cells for CAR-T cohort; stem cells for alloSCT cohort)					x							
Lymphodepleting Chemotherapy (CAR-T Therapy Cohort)		x	x									
Conditioning Chemotherapy (Allogeneic Stem Cell Transplant Cohort)		x	x									
Concomitant Medications	Continuous											
Adverse Events	Continuous											
Ascertainment of adverse events of special interest				x						x		
Ascertainment of adverse events related to cellular therapy <sup>1</sup>								x			x	
Review of standard of care bloodwork including for all inclusion criteria including Hepatitis B sAg, sAb, cAb, Hepatitis C, HIV testing including viral load and CD4 count if HIV positive, HBV viral DNA if Hepatitis B sAg positive and HCV viral DNA if Hepatitis C antibody positive, and pregnancy testing if applicable <sup>10</sup>	x											
Review of standard of care hematology bloodwork		x						x				

Bloodwork (serum) for regulatory requirements to bank for routine safety testing post FMT if required		x						x				
Bloodwork (plasma, PBMC) for exploratory studies		x						x			x	x
Urine sample for exploratory studies		x						x			x	
Stool sample		x <sup>11</sup>						x <sup>11</sup>			x	
Rectal swab for regulatory requirements, to bank for routine safety testing post FMT if required <sup>12</sup>		x						x				
Rectal swab for research purposes <sup>12</sup>		x						x			x	
Review of standard of care disease assessment – B-cell lymphoma <sup>3</sup>	x <sup>4</sup>							x			x	x
Review of standard of care disease assessment – MDS <sup>5</sup>	x <sup>6</sup>							x			x	
Review of standard of care disease assessment – AML <sup>7</sup>	x <sup>6</sup>							x			x	

<sup>1</sup> MDS/AML: Location and maximal grade of acute GVHD will be assessed from Day 0 (alloSCT) until Day +100. B-cell lymphoma: CRS and ICANS events will be documented according to maximal grade for the first 30 days after cell therapy.

<sup>2</sup> + up to 30 days if no recovery of neutropenia (ANC must be  $\geq 1.0 \times 10^9/L$  without reliance on growth factors for a 7 day period to administer FMT, and ANC must be documented within 7 days prior to administration) If patients remain reliant on growth factors, the second FMT series will be delayed by a maximum of 30 days, after which time it will be omitted. Additionally, patients must not have any signs, symptoms, or documented clinical infection at the time of second FMT series.

<sup>3</sup> Clinical chart review of standard of care documentation of disease response at Day +30, Day +90 and Day +180 post cell therapy, based on Lugano 2014 classification criteria from PET scan assessment

<sup>4</sup> Baseline disease assessment scan will be the scan done most recently prior to cellular therapy administration.

<sup>5</sup> Clinical chart review of standard of care documentation of disease response at day +100 bone marrow and peripheral blood assessment, using MDS International Working Group 2023 criteria.

<sup>6</sup> Baseline bone marrow and peripheral blood assessment will be the most recent testing done prior to cellular therapy administration.

<sup>7</sup> Clinical chart review of standard of care documentation of disease response at day +100 bone marrow and peripheral blood assessment, using European Leukemia Network criteria.

<sup>8</sup> Protocol treatment should begin within 7 working days of patient enrollment. Patients must have an ANC  $\geq 1.0 \times 10^9/L$  without growth factor support, documented within 7 days prior to both the first and second FMT administrations.

<sup>9</sup> Consent should be done prior to any screening assessments and according to site institutional timelines. Site should follow their institutional guidelines for consenting window prior to FMT administration. Informed consent of study procedures may be obtained prior to the 60-day screening window. Subject enrollment with Ozmosis@UHN is required. Please refer to section 3.1.3 Enrollment Procedures.

<sup>10</sup> Screening laboratory testing to be done within 60 day screening window prior to starting FMT administration or registration; hemoglobin, platelet count, neutrophil count, AST/ALT, and creatinine. The most recent labs prior to FMT administration will be used for screening.

<sup>11</sup> Participants will be asked to collect stool at home 24 hours prior to starting their bowel prep for the FMT procedure.

<sup>12</sup> Rectal swab(s) will be performed by research nurse on day of visit

## DATA REPORTING / REGULATORY REQUIREMENTS

### 9.1 Compliance with Trial Registration and Results Posting Requirements

Prior to the first subject being registered/enrolled into this study, the Sponsor will be responsible for ensuring that the clinical trial is registered appropriately to remain eligible for publication in any major peer-reviewed journal, adhering to the guidelines put forth by the International Committee of Medical Journal Editors (ICMJE). Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

### 9.2 Patient Protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West, Edinburgh Washington, Tokyo, Seoul and Fortaleza amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice..<sup>50</sup> The protocol will be approved by the Research Ethics Board (REB) and Health Canada.

### 9.3 Data Collection and Reporting

All data obtained in the clinical trial described in this protocol will be reported on eCRFs in the Medidata Electronic Document Capture system (Medidata). Data reported on eCRFs should be consistent with the source documents and verifiable.

Please see the study specific eCRF Completion Guidelines which have been provided to your site by Ozmosis Research Inc. The timelines and details for completion of eCRFs are included in these guidelines.

All data for the primary and secondary endpoints will source verified prior to publication. The Investigator will review the data and electronically sign the eCRFs to acknowledge agreement with the data entered. Data will be entered into Medidata will be used for developing tables and listings for the final study report.

### 9.4 Subject Confidentiality and Access to Source Data/Documents

Any research information obtained about the subject in this study will be kept confidential. A subject will not be identified by name, only by his/her study ID code. The subject's name or any identifying information will not appear in any reports published as a result of this study.

However, information obtained from individual subject's participation in the study may be disclosed with his/her consent to the health care providers for the purpose of obtaining appropriate medical care. In accordance with federal regulations and GCP guidelines, the investigator should make available for direct access all trial-related records upon request of the

sponsor, Ozmosis Research, auditor, REB or Health Canada. This is for the purpose of verifying information obtained for this study. Confidentiality will be maintained throughout the study within the limits of the law.

A subject's name will not be given to anyone except the researchers conducting the study, who have pledged an oath of confidentiality. All identifying information will be kept behind locked doors, under the supervision of the study Principal Investigator and will not be transferred outside of the hospital.

A subject may take away his/her permission to collect, use and share information about him/her at any time. If this situation occurs, the subject will not be able to remain in the study. No new information that identifies the subject will be gathered after that date. However, the information about the subject that has already been gathered and transferred may still be used and given to others as described above in order to preserve the scientific integrity and quality of the study.

#### 9.5 Study Monitoring/Auditing

Data generated as a result of this study are to be available for inspection on request by local health authority auditors, the Sponsor's Study Monitors and other personnel (as appropriate) and by the REB. The Investigator shall permit sponsor, authorized agents of the sponsor, CRO and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held, and to inspect all source documents. The protocol and other study documents contain confidential information and should not be shared or distributed without the prior written permission of sponsor.

#### 9.6 Study Monitoring/Auditing

This is an investigator-initiated study and study monitoring will be performed by Ozmosis Research Inc. Ozmosis Research Inc. will organize site monitoring for this study to be conducted as per the monitoring plan.

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by the Health Products and Food Branch Inspectorate. Other audits may be conducted by the study sponsor or Ozmosis Research Inc.

#### 9.7 Quality Control and Quality Assurance

As per the Guidelines of Good Clinical Practice, the sponsor will be responsible for implementing and maintaining quality assurance and quality control systems.

## 9.8 Data Management Guidelines

The Eligibility Checklist will be a paper CRF.

### 9.8.1 Case Report Form Completion

The paper Eligibility Checklist CRF must be completed using black or blue ink. Any errors must be crossed out so that the original entry is still visible, the correction clearly indicated and then initialed and dated by the individual making the correction. eCRFs will be completed according to the Study Calendar.

## 9.9 REB Composition

The composition of the REB will be kept on file. The composition and procedures of the REB must be compliant with the ICH-GCP Guidelines and be consistent with Canadian regulatory requirements.

### 9.10 Initial Approval

All study sites are required to obtain full board ethics approval of the protocol and consent form by the appropriate ethics board prior to commencement of the clinical trial at each site.

### 9.11 Annual Re-Approvals

Annual (or as required by the ethics board) re-approval may be required for as long as patients are being followed on protocol. It will be the Principal Investigator's responsibility to apply for and obtain the re-approval.

### 9.12 Amendments / Revisions

All protocol amendments will be confirmed in writing and submitted, as appropriate, for review by the ethics board and health authorities. Amendments will be reviewed and approved by Health Canada prior to central implementation of the study, and by REB prior to local implementation, EXCEPT when the amendment eliminates an immediate hazard to clinical trial patients or when the change(s) involve(s) only logistical or administrative aspects of the trial.

### 9.13 REB Refusals

If an REB refuses to approve this protocol (or an amendment/revision to this protocol), Ozmosis Research Inc. must be notified immediately of the date of refusal and the reason(s) for the refusal.

### 9.14 Serious Adverse Events, Safety Updates, and Investigator Brochure Updates

During the course of the study SAEs, safety updates or investigator brochure updates may be sent to sites for reporting to their ethics board. If/when this occurs documentation of ethics board submission must be forwarded to Ozmosis.

### 9.15 Informed Consent Document

The REB must approve the consent form document which will be used prior to its local activation; changes to the consent form in the course of the study will also require REB notification/approval.

The consent form should include all elements required by ICH-Good Clinical Practice Guidelines.

### 9.16 Consent Process/ Patient Eligibility

Patients who cannot give informed consent (i.e. mentally incompetent patients, or those physically incapacitated such as comatose patients) are not to be recruited into the study. Patients competent but physically unable to sign the consent form may have the document signed by their nearest relative or legal guardian. Each patient will be provided with a full explanation of the study before consent is requested.

### 9.17 Site and Study Closure

Upon completion of the study, the following activities, when applicable, will be completed:

- Collection of study materials (i.e., specimen collection kits, drug shippers, etc.)
- Data clarifications and/or resolutions
- Review of site study records for completeness

If the Sponsor or Investigator or appropriate regulatory officials identify conditions arising during the study that indicate that the study should be halted, this action may be taken after appropriate consultation with the Investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the patients enrolled in the study.
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.
- Failure of the Investigator to enroll patients into the study at an acceptable rate.
- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities.
- Submission of knowingly false information to the Sponsor, or appropriate regulatory authority.
- Insufficient adherence to protocol requirements.
- Refusal of the Investigator to supply source documentation of work performed in this clinical trial.

Study termination and follow-up will be performed in compliance with the conditions set forth in the International Conference on Harmonization (ICH) sixth efficacy publication (E6) on Good Clinical Practice, Section 4.12, ICH E6 4.13, ICH E6 5.20, and ICH E6 5.21.

## 10. STATISTICAL CONSIDERATIONS

### 10.1 Study Design/Endpoints

This is a single centre, non-randomized, single-arm interventional pilot study in patients undergoing CAR-T or allogeneic stem cell transplantation (alloSCT).

The primary endpoints are feasibility and safety.

We hypothesize that we will be able to successfully recruit at least 50% of approached patients, retain at least 80% of patients on the study, and successfully administer at least one FMT series to 80% of retained patients. We also hypothesize that FMT will be safe in this population. Each cohort will be considered separately in considering the differing risks of CAR-T and alloSCT. We hypothesize that in each cohort there will be no greater than 10% incidence ( $N \leq 1$  of 10 participants in each cohort), of serious adverse events, or Grade  $\geq 3$  adverse events of special interest (sepsis and/or bacteremia, ICU admission, bowel perforation, or death) within 48 hours of administration of FMT, which are judged to be possibly, probably or definitely related to FMT.

The primary endpoints will be analyzed using descriptive statistical methods in the safety-evaluable population, which consists of all subjects who receive any amount of FMT treatment. Each disease type (B-cell lymphoma and AML/MDS) will also be analyzed separately.

### 10.2 Sample size/Accrual Rate

Since no preliminary information on the primary endpoints in previous relevant studies/literature are available for sample size justification, for this pilot study, we will enroll a convenient sample size of 20 eligible patients.

### 10.3 Secondary Endpoints

The secondary endpoints such as the incidence of AEs, response rates will be summarized using descriptive statistical methods. The time to event endpoints, eg, progression-free survival (PFS), overall survival (OS), will be analyzed using Kaplan-Meier method.

### 10.4 Exploratory Endpoints

An exploratory safety endpoint will include the finding of any newly acquired antibiotic resistant organism during the time period of follow up. If a new ARO is found, the FMT product will be retrospectively analysed to determine if it might be related to the ARO, as it is possible the recipient may also have acquired the ARO from health care contact.

For microbial safety endpoints, DNA will be extracted from stool using the Qiagen PowerSoil kits prior to bacterial density quantitation (by 16S rRNA gene qPCR). A two-stage sample analysis will be performed with 16S rRNA gene amplicon sequencing for composition, followed by sequencing to optimize depth to detect/assess donor species/strain relative abundance based

on genus relative abundance determined from 16S rRNA sequencing (i.e. with variable sequencing depth for optimal sensitivity based on 16S analysis). Alpha diversity (Shannon diversity index, taxonomic richness, Berger-Parker dominance) will be calculated on tables rarefied to control for sampling depth. Compositional dissimilarity/similarity (beta-diversity) will be assessed between groups and sample pairs (i.e. pre/post intervention or donor/recipient) using Bray-Curtis compositional dissimilarity. Functional outcomes will be studied using shotgun metagenomic sequencing and targeted gene detection to assess for aspects including but not limited to antimicrobial gene richness, abundance and diversity, butyrate biosynthesis gene abundance, stool versus urine and plasma short-chain fatty acids and 1° bile acid (BA)/2°BA concentrations. Blood will also analyzed for T-cell phenotypic and functional subsets and diversity, and via flow for anti-FMT bacterial antibodies as a correlate of engraftment and immunogenicity. Methods are established in the Coburn Laboratory.<sup>51-53</sup>

Patient reported perceptions and experience with FMT will be reported in a descriptive manner.

#### 10.5 Missing Data Handling

No imputation of values for missing data will be performed except that missing or partial start and end dates for AEs and concomitant medication will be imputed according to pre-specified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation. Any deviation from the original statistical plan will be described in the final report.

## 11. DOCUMENTATION, RECORD ACCESS AND MAINTENANCE OF STUDY RECORDS

### 11.1 Documentation of Patient's Participation

A statement acknowledging the participation of a patient in this clinical trial must be documented in the patient's medical records along with the signed ICF.

### 11.2 Regulatory Requirements

The following documents are required:

- For participating Canadian sites only:
  - All Principal Investigators must complete and sign the Health Canada Qualified Investigator Undertaking form. The completed forms must be returned to Ozmosis prior to any drug shipment.
  - Ozmosis will submit a completed Health Canada Clinical Trial Site Information Form to Health Canada after local activation of each participating Canadian site.
- All applicable regulatory documents as listed in the Site Activation Checklist provided by Ozmosis to the sites.
- A copy of the initial full board approval letter from the ethics board. Continuing approval (full board) will be obtained at least yearly until follow-up on patients is completed and no further data is being obtained for research purpose.

### 11.3 Patient Confidentiality and Access to Source Data/Documents

Any research information obtained about the patient in this study will be kept confidential. A patient will not be identified by name. The patient's name or any identifying information will not appear in any reports published as a result of this study.

However, information obtained from the patients participation in the study may be disclosed with their consent to the health care providers for the purpose of obtaining appropriate medical care. The patients medical records/charts, tests will be made available to Ozmosis, the Sponsor's partners, the Canadian regulatory authority Health Canada, the ethics boards and any other regulatory authorities. This is for the purpose of verifying information obtained for this study. Confidentiality will be maintained throughout the study within the limits of the law.

A patient's name will not be given to anyone except the researchers conducting the study, who have pledged an oath of confidentiality. All identifying information will be kept behind locked doors, under the supervision of the study Principal Investigator and will not be transferred outside of the hospital.

A patient may take away their permission to collect, use and share information about them at any time. If this situation occurs, the patient will not be able to remain in the study. No new information that identifies the patient will be gathered after that date. However, the information about the patient that has already been gathered and transferred may still be used and given to others as described above in order to preserve the scientific integrity and quality of the study.

#### 11.4 Confidentiality of the Study

Data generated as a result of this study are to be available for inspection on request by local health authority auditors, the Sponsor's Study Monitors and other personnel (as appropriate) and by the ethics board. The Principal Investigator shall permit the Sponsor, authorized agents of the Sponsor, CRO and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held, and to inspect all source documents. The protocol and other study documents contain confidential information and should not be shared or distributed without the prior written permission of the Sponsor.

#### 11.5 Study Data at the End of Registration of Clinical Trial

Prior to the first patient being enrolled into this study, the Sponsor will be responsible for ensuring that the clinical trial is registered (e.g. [clinicaltrials.gov](http://clinicaltrials.gov)) appropriately to remain eligible for publication in any major peer-reviewed journal, adhering to the guidelines put forth by the International Committee of Medical Journal Editors (ICMJE).

#### 11.6 Data Reporting

*The data will be collected in eCRFs using a Medidata database.*

#### 11.7 Maintenance of Study Records

To enable evaluations and/or audits from regulatory authorities, Ozmosis or the Sponsor, the Principal Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eCRFs and hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of treatment disposition. The Principal Investigator should retain these records for 15 years after study close-out as required by Canadian regulations or as specified in the Clinical Trial Agreement, whichever is longer

If the Principal Investigator relocates, retires, or for any reason withdraws from the study, then the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Site Investigator, another institution, or to the Sponsor. The Principal Investigator must obtain the Sponsor's written permission before disposing of any records.

## 12. ADMINISTRATIVE PROCEDURES

### 12.1 Amendments to the Protocol

Modifications of the signed protocol are only possible by approved protocol amendments authorized by the sponsor. All protocol amendments will be approved by the REB prior to implementation. The Investigator must not implement any deviation from, or change to the protocol, except where it is necessary to eliminate an immediate hazard to trial subjects or when the change(s) involves only logistical administrative aspects of the trial.

### 12.2 Protocol Deviations and Violations

All violations or deviations are to be reported to the site's REB (as per REB guidelines). All REB correspondence is to be forwarded to Ozmosis Research. The site must notify Ozmosis Research and/or sponsor immediately of any protocol violations.

### 12.3 Premature Discontinuation of the Study

The Sponsor reserves the right to discontinue the trial for any reason but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigators must contact all participating patients immediately after notification. Standard therapy and follow-up for subjects will be assured and, where required by the applicable regulatory requirement(s), the relevant regulatory authority(ies) will be informed.

The REB will be informed promptly and provided with a detailed written explanation for the termination or suspension.

As directed by the Sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

## 13. LEGAL ASPECTS

### 13.1 Publication Policies and Disclosure of Data

For publications, the first author will be the Principal Investigator of the study. Additional authors will be those who have made the most significant contribution to the overall success of the study. This contribution will be reviewed at the end of the trial by the Principal Investigator.

## REFERENCES

1. Neelapu SS, Jacobson CA, Ghobadi A, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. *Blood*. 2023;141(19):2307-2315.
2. Neelapu SS, Chavez JC, Sehgal AR, et al. Three-year follow-up analysis of axicabtagene ciloleucel in relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5). *Blood*. 2024;143(6):496-506.
3. Westin JR, Oluwole OO, Kersten MJ, et al. Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma. *N Engl J Med*. 2023;389(2):148-157.
4. Abramson JS, Palomba ML, Gordon LI, et al. Two-year follow-up of lisocabtagene maraleucel in relapsed or refractory large B-cell lymphoma in TRANSCEND NHL 001. *Blood*. 2024;143(5):404-416.
5. Abramson JS, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. *Blood*. 2023;141(14):1675-1684.
6. Wang M, Munoz J, Goy A, et al. Three-Year Follow-Up of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma, Including High-Risk Subgroups, in the ZUMA-2 Study. *J Clin Oncol*. 2023;41(3):555-567.
7. Yamshon S, Gribbin C, Alhomoud M, et al. Safety and Toxicity Profiles of CAR T Cell Therapy in Non-Hodgkin Lymphoma: A Systematic Review and Meta-Analysis. *Clin Lymphoma Myeloma Leuk*. 2024;24(6):e235-e256 e232.
8. Greinix HT, Eikema DJ, Koster L, et al. Improved outcome of patients with graft-versus-host disease after allogeneic hematopoietic cell transplantation for hematologic malignancies over time: an EBMT mega-file study. *Haematologica*. 2022;107(5):1054-1063.
9. Viaud S, Saccheri F, Mignot G, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. *Science*. 2013;342(6161):971-976.
10. Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science*. 2018;359(6371):97-103.
11. Andrews MC, Duong CPM, Gopalakrishnan V, et al. Gut microbiota signatures are associated with toxicity to combined CTLA-4 and PD-1 blockade. *Nat Med*. 2021;27(8):1432-1441.
12. Matson V, Fessler J, Bao R, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science*. 2018;359(6371):104-108.
13. Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science*. 2018;359(6371):91-97.
14. Vetizou M, Pitt JM, Daillere R, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science*. 2015;350(6264):1079-1084.
15. Peled JU, Gomes ALC, Devlin SM, et al. Microbiota as Predictor of Mortality in Allogeneic Hematopoietic-Cell Transplantation. *N Engl J Med*. 2020;382(9):822-834.
16. Smith M, Dai A, Ghilardi G, et al. Gut microbiome correlates of response and toxicity following anti-CD19 CAR T cell therapy. *Nat Med*. 2022;28(4):713-723.
17. Hu Y, Li J, Ni F, et al. CAR-T cell therapy-related cytokine release syndrome and therapeutic response is modulated by the gut microbiome in hematologic malignancies. *Nat Commun*. 2022;13(1):5313.

18. Stein-Thoeringer CK, Saini NY, Zamir E, et al. A non-antibiotic-disrupted gut microbiome is associated with clinical responses to CD19-CAR-T cell cancer immunotherapy. *Nat Med*. 2023;29(4):906-916.
19. Minkoff NZ, Aslam S, Medina M, et al. Fecal microbiota transplantation for the treatment of recurrent *Clostridioides difficile* (*Clostridium difficile*). *Cochrane Database Syst Rev*. 2023;4(4):CD013871.
20. Fattizzo B, Cavallaro F, Folino F, Barcellini W. Recent insights into the role of the microbiome in malignant and benign hematologic diseases. *Crit Rev Oncol Hematol*. 2021;160:103289.
21. Kelly CR, Kahn S, Kashyap P, et al. Update on Fecal Microbiota Transplantation 2015: Indications, Methodologies, Mechanisms, and Outlook. *Gastroenterology*. 2015;149(1):223-237.
22. Hamilton MJ, Weingarden AR, Unno T, Khoruts A, Sadowsky MJ. High-throughput DNA sequence analysis reveals stable engraftment of gut microbiota following transplantation of previously frozen fecal bacteria. *Gut Microbes*. 2013;4(2):125-135.
23. Khan MY, Dirweesh A, Khurshid T, Siddiqui WJ. Comparing fecal microbiota transplantation to standard-of-care treatment for recurrent *Clostridium difficile* infection: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol*. 2018;30(11):1309-1317.
24. Quraishi MN, Widlak M, Bhala N, et al. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory *Clostridium difficile* infection. *Aliment Pharmacol Ther*. 2017;46(5):479-493.
25. DeFilipp Z, Bloom PP, Torres Soto M, et al. Drug-Resistant *E. coli* Bacteremia Transmitted by Fecal Microbiota Transplant. *N Engl J Med*. 2019;381(21):2043-2050.
26. Kelly CR, Yen EF, Grinspan AM, et al. Fecal Microbiota Transplantation Is Highly Effective in Real-World Practice: Initial Results From the FMT National Registry. *Gastroenterology*. 2021;160(1):183-192 e183.
27. Rashidi A, Ebadi M, Rehman TU, et al. Randomized Double-Blind Phase II Trial of Fecal Microbiota Transplantation Versus Placebo in Allogeneic Hematopoietic Cell Transplantation and AML. *J Clin Oncol*. 2023;41(34):5306-5319.
28. Malard F, Loschi M, Huynh A, et al. Pooled allogeneic faecal microbiota MaaT013 for steroid-resistant gastrointestinal acute graft-versus-host disease: a single-arm, multicentre phase 2 trial. *EClinicalMedicine*. 2023;62:102111.
29. Bilinski J, Grzesiowski P, Sorensen N, et al. Fecal Microbiota Transplantation in Patients With Blood Disorders Inhibits Gut Colonization With Antibiotic-Resistant Bacteria: Results of a Prospective, Single-Center Study. *Clin Infect Dis*. 2017;65(3):364-370.
30. DeFilipp Z, Peled JU, Li S, et al. Third-party fecal microbiota transplantation following allo-HCT reconstitutes microbiome diversity. *Blood Adv*. 2018;2(7):745-753.
31. Kakihana K, Fujioka Y, Suda W, et al. Fecal microbiota transplantation for patients with steroid-resistant acute graft-versus-host disease of the gut. *Blood*. 2016;128(16):2083-2088.
32. Qi X, Li X, Zhao Y, et al. Treating Steroid Refractory Intestinal Acute Graft-vs.-Host Disease With Fecal Microbiota Transplantation: A Pilot Study. *Front Immunol*. 2018;9:2195.

33. van Lier YF, Davids M, Haverkate NJE, et al. Donor fecal microbiota transplantation ameliorates intestinal graft-versus-host disease in allogeneic hematopoietic cell transplant recipients. *Sci Transl Med*. 2020;12(556).
34. Shouval R, Geva M, Nagler A, Youngster I. Fecal Microbiota Transplantation for Treatment of Acute Graft-versus-Host Disease. *Clin Hematol Int*. 2019;1(1):28-35.
35. Battipaglia G, Malard F, Rubio MT, et al. Fecal microbiota transplantation before or after allogeneic hematopoietic transplantation in patients with hematologic malignancies carrying multidrug-resistance bacteria. *Haematologica*. 2019;104(8):1682-1688.
36. Ghani R, Mullish BH, McDonald JAK, et al. Disease Prevention Not Decolonization: A Model for Fecal Microbiota Transplantation in Patients Colonized With Multidrug-resistant Organisms. *Clin Infect Dis*. 2021;72(8):1444-1447.
37. Innes AJ, Mullish BH, Fernando F, et al. Faecal microbiota transplant: a novel biological approach to extensively drug-resistant organism-related non-relapse mortality. *Bone Marrow Transplant*. 2017;52(10):1452-1454.
38. Spindelboeck W, Schulz E, Uhl B, et al. Repeated fecal microbiota transplantations attenuate diarrhea and lead to sustained changes in the fecal microbiota in acute, refractory gastrointestinal graft-versus-host-disease. *Haematologica*. 2017;102(5):e210-e213.
39. Kaito S, Toya T, Yoshifuji K, et al. Fecal microbiota transplantation with frozen capsules for a patient with refractory acute gut graft-versus-host disease. *Blood Adv*. 2018;2(22):3097-3101.
40. Biernat MM, Urbaniak-Kujda D, Dybko J, Kapelko-Slowik K, Prajs I, Wrobel T. Fecal microbiota transplantation in the treatment of intestinal steroid-resistant graft-versus-host disease: two case reports and a review of the literature. *J Int Med Res*. 2020;48(6):300060520925693.
41. Mao D, Jiang Q, Sun Y, et al. Treatment of intestinal graft-versus-host disease with unrelated donor fecal microbiota transplantation capsules: A case report. *Medicine (Baltimore)*. 2020;99(38):e22129.
42. Douge A, Ravinet A, Corriger A, et al. Faecal microbiota transplantation to prevent complications after allogeneic stem cell transplantation for haematological malignancies: a study protocol for a randomised controlled phase-II trial (the FMT-allo study). *BMJ Open*. 2023;13(5):e068480.
43. Carreira AS, Salas MQ, Remberger M, et al. Bloodstream Infections and Outcomes Following Allogeneic Hematopoietic Cell Transplantation: A Single-Center Study. *Transplant Cell Ther*. 2022;28(1):50.e51-50.e58.
44. S Anwer JF, B Hamandi, R Guang-Ye Jin, M Kisson, A Paterson, S Hota, S Poutanen. Determination of Optimal Duration and Conditions for Long-Term Storage of Fecal Filtrate Samples Used for Fecal Microbiota Transplants (FMT) and Microbiota Research. *ASM Microbe*; 2022; Washington, DC.
45. Guidance Document: Fecal Microbiota Therapy Used in the Treatment of Clostridium difficile Infection Not Responsive to Conventional Therapies. Ottawa: Health Canada; 2015.
46. Hota SS, Sales V, Tomlinson G, et al. Oral Vancomycin Followed by Fecal Transplantation Versus Tapering Oral Vancomycin Treatment for Recurrent Clostridium difficile Infection: An Open-Label, Randomized Controlled Trial. *Clin Infect Dis*. 2017;64(3):265-271.

47. Shahid Z, Etra AM, Levine JE, et al. Defining and Grading Infections in Clinical Trials Involving Hematopoietic Cell Transplantation: A Report From the BMT CTN Infectious Disease Technical Committee. *Transplant Cell Ther.* 2024;30(5):540.e541-540.e513.
48. Lee DW, Santomaso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biology of Blood and Marrow Transplantation.* 2019;25(4):625-638.
49. Harris AC, Young R, Devine S, et al. International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. *Biol Blood Marrow Transplant.* 2016;22(1):4-10.
50. The International Council for Harmonisation, Efficacy Guidelines, Good Clinical Practice. 2019; <https://www.ich.org/page/efficacy-guidelines#6>.
51. Rooney AM, Cochrane K, Fedsin S, et al. A microbial consortium alters intestinal Pseudomonadota and antimicrobial resistance genes in individuals with recurrent *Clostridioides difficile* infection. *mBio.* 2023;14(4):e0348222.
52. Rooney AM, Raphenya AR, Melano RG, et al. Performance Characteristics of Next-Generation Sequencing for the Detection of Antimicrobial Resistance Determinants in *Escherichia coli* Genomes and Metagenomes. *mSystems.* 2022;7(3):e0002222.
53. Spreafico A, Heirali AA, Araujo DV, et al. First-in-class Microbial Ecosystem Therapeutic 4 (MET4) in combination with immune checkpoint inhibitors in patients with advanced solid tumors (MET4-IO trial). *Ann Oncol.* 2023;34(6):520-530.