EXPANDED FECAL MICROBIOTA TRANSPLANTATION USE FOR THE TREATMENT OF CLOSTRIDIOIDES DIFFICILE: A STUDY OF THE ECONOMIC AND POLICY IMPLICATIONS

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ABSTRACT

Problem Statement: Patients and clinicians face a dire need for access to effective treatments for diseases with treatment-resistant colitis and diarrhea. An efficacious treatment—fecal microbiota transplant—exists but is currently considered third-line therapy in the United States and has limited access due to current U.S. policies and regulations.

Methods: This research used a systematic literature review and key informant interviews to identify key issues and barriers in gut biome research, discuss the potential for fecal microbiota transplantation (FMT) as a treatment option, identify other innovative treatments for gut-mediated illness, and evaluate the policies and procedures regulating and impacting the use of FMT. An economic model was developed to explore the cost-effectiveness of expanded use of FMT to treat clostridium difficile infection (CDI) in the United States, as compared to current standard treatment options.

Results: A process diagram describes the steps and components that comprise the complete FMT lifecycle, the relevant policy and regulatory governance and oversight in each step, the economic impact, and the stakeholders involved throughout. The systematic literature review showed that although FMT is widely used globally and microbiota therapies are growing, there is not a consistent, widely accepted policy and regulatory approach to stool as a therapeutic treatment. Economic model results showed that the cost effectiveness of CDI and recurrent CDI (rCDI) treatment is largely driven by the efficacy and cost of currently available antibiotics; unless there is a significant decline in antibiotic effectiveness and a significant drop in the cost of FMT, standard antibiotic therapy is the most cost-effective treatment option.

Conclusion: FMT and microbiota therapy are promising novel treatment options that will likely become more widely used as understanding of the role of the microbiome in the immune system grows and as the need for non-antibiotic therapies increases. More research is needed on the safety and efficacy of

FMT, including unintended and long-term effects, before widespread adoption. The current regulatory framework is not flexible enough to adapt to rapid advances in innovative treatment options, and the risks of declining efficacy of antibiotics in the future necessitates advances in innovative treatment options now.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACG	American College of Gastroenterology
ADL	Activities of Daily Living
AHRQ	Agency for Healthcare Research and Quality
CA-CDI	Community-associated CDI
c. diff	*Clostridioides difficile.* The bacterium Clostridium difficile was renamed Clostridioides difficile in August 2016.
CAR-T	chimeric antigen receptor T-cell
CDC	Centers for Disease Control and Prevention
CDI	*Clostridioides difficile* infection
CLIA	Clinical Laboratory Improvement Amendments
CMS	Center for Medicare and Medicaid Services
CO-HCFA	Community onset healthcare facility associated
COVID-19	Coronavirus Disease 2019
DALY	Disability Adjusted Life Years
DIY	Do-it-yourself
E. coli	Escherichia coli
EIP	Emerging Infections Program
EUG	EU Gastrointestinal
ESCMID	European Society for Clinical Microbiology and Infectious Diseases
EUTCD	European Tissue and Cells Directive
FDA	Food and Drug Administration
FDX	Fidaxomicin
FMT	Fecal microbiota transplantation (or transplant)
GDP	Gross Domestic Product
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HAC	Hospital Acquired Condition
HAI	Healthcare-Associated Infection(s)
HAIC	Healthcare-Associated Infections Community Interface
HCPCS	Healthcare Common Procedural Coding System
HIPAA	Health Insurance Portability and Accountability Act
HMP	Human Microbiome Project
HO-CDI	Healthcare Facility Onset CDI
HRQoL	Health-related Quality of Life
IBD	Inflammatory bowel disease
ICER	Incremental Cost Effectiveness Ratio
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
IHME	Institute for Health Metrics and Evaluation
IND	Investigational New Drug
IRB	Institutional Review Board

IV	Intravenously
LTCF	Long Term Care Facility
MeSH	Medical Subject Headings
MDRO	Multi drug resistant organism(s)
NAAT	Nucleic acid amplification test
NHSN	National Healthcare Safety Network
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NMB	Net Monetary Benefit
NQF	National Quality Forum
OHRP	Office for Human Research Protections
OOP	Out of Pocket
PCR	Polymerase chain reaction
PO	By mouth
PR	By rectum
QALY	Quality Adjusted Life Years
rCDI	Recurrent (or refractory) *Clostridioides difficile* infection
RCT	Randomized control trial
SARS-CoV2	Severe Acute Respiratory Syndrome Coronavirus 2
SHEA	Society for Healthcare Epidemiology of America
UC	Ulcerative colitis
UK	United Kingdom
U.S.	United States
USD	U.S. Dollars
VAN	Vancomycin
WHO	World Health Organization
WTP	Willingness to Pay
YLD	Years Lost to Disability
YLL	Years of Life Lost

CHAPTER 1: INTRODUCTION

BACKGROUND

Patients and clinicians face a dire need for access to effective treatments for treatment-resistant colitis and diarrhea. An efficacious treatment—fecal microbiota transplant—exists but is currently considered third-line therapy in the United States (U.S) and has limited access and utilization due to current U.S. policies and regulations. This research will explore the policy and economic implications of expanded use of fecal microbiota transplant as a treatment option using *Clostridioides difficile* infection as a use case.

The Microbiome

Bacterial cells on the human body outnumber human cells by three to ten times, but only make up one to three percent of our body mass; for every gene in the human genome, humans harbor approximately 1,000 bacterial genes. Bacteria play significant roles in human bodily processes and functions, but are only beginning to be understood; the Human Genome Project only published the first version of the human genome in 2001, and the Human Microbiome Project was established in 2008 "with the mission of generating resources that would enable the comprehensive characterization of the human microbiome and analysis of its role in human health and disease."(International Human Genome Sequencing et al., 2001; "NIH Common Fund Human Microbiome Project (HMP) ", 2008; "An Overview of the Human Genome Project," 2016)

Rapid and recent advances in clinical genomics have enabled scientists to begin to identify and understand the key roles and interactions that bacteria have in the human body. The bacteria colonizing our digestive tracts, or the gut microbiome, make up a complicated and dynamic ecosystem that is implicated in many diseases and important functions. Some are more obvious gastrointestinal diseases,

like inflammatory bowel disease (IBD) including Crohn's, ulcerative colitis (UC), and irritable bowel syndrome (IBS), but also include those as varied as asthma, cardiac conditions, obesity, diabetes, Parkinson's, autoimmune functions, and mental health.(Fujimura & Lynch, 2015; Holt, Cockram, Flyvbjerg, & Goldstein, 2017; Huang & Boushey, 2015; Knights, Lassen, & Xavier, 2013; Kostic, Xavier, & Gevers, 2014; Michail et al., 2011; Morgan et al., 2012; Rieder, Wisniewski, Alderman, & Campbell, 2017; Riiser, 2015; Tang, Kitai, & Hazen, 2017; Tremlett, Bauer, Appel-Cresswell, Finlay, & Waubant, 2017; Wright et al., 2015)

Clostridioides difficile

Gut dysbiosis can occur when the types and concentrations of bacteria in the gut are disturbed and imbalanced. This can lead to altered, impaired, or poor functioning of the gut. One severe type of gut dysbiosis is from the infection of *Clostridioides difficile*. *Clostridioides difficile* (*c. diff*) is an anaerobic Gram-positive bacteria that produces spores in the intestine and causes colitis.

As a diarrheal disease, *Clostridioides difficile* infection (CDI) causes half a million infections per year and is associated with significant morbidity and mortality both in healthcare facilities and in the community.(Lessa et al., 2015) CDI is the most common healthcare associated infection (HAI) in the Unites States and "the leading cause of gastroenteritis-associated death;" it costs nearly $5 billion in excess costs annually for acute care facilities and has a 30-day mortality rate of almost 10%.(Lessa et al., 2015) CDI is an epidemic in nursing homes and hospitals.(Dubberke & Olsen, 2012; Hunter et al., 2016; Lessa et al., 2015) Only approximately 24% of CDI acquired in healthcare facilities have hospital onset; the majority of infections are diagnosed and addressed in the community and ancillary facilities, which presents significant additional burden in the healthcare system.(Dubberke & Olsen, 2012; Lessa et al., 2015) Further, patients report a significant negative impact to their health-related quality of life (HRQoL) from CDI.(Guillemin et al., 2014; Pakyz, Moczygemba, VanderWielen, & Edmond, 2016)

While *c. diff* bacteria are not significantly antibiotic resistant to current treatment methods, antibiotic use is "a dominant risk for the development of CDI."(Bartlett & Perl, 2005; DePestel & Aronoff, 2013; Spigaglia, 2016) In a 2013 CDC report on the threat of antibiotic resistance, *c. diff* was one of three organisms included in the category of threat level of "Urgent" "because of its unique relationship with resistance issues, antibiotic use, and its high morbidity and mortality."

One innovative and novel treatment option for CDI is the use of fecal microbiota transplantation (FMT), in which a patient is treated for gut dybiosis from CDI with the bacteria from another healthy patient's stool. FMT is an alternative or supplementary treatment option, used in place of or in addition to antibiotics, when traditional antibiotic therapy is no longer a curative option.

Fecal Microbiota Transplant

Fecal microbiota transplantation, or transplant, (FMT) is the process by which donor stool is mixed with saline to create a slurry and transplanted typically via colonoscopy to the recipient's intestines.(Lawrence J Brandt et al., 2012; Gough, Shaikh, & Manges, 2011) The purpose of an FMT is to replace and replenish the recipient's disrupted or infected gut microbiome in the GI tract with a mix of healthy donor bacteria to cure disease or promote health. FMT has been around since the 4th century and is used in veterinary medicine but has regained popularity in Western medicine for the treatment of gastrointestinal (GI) diseases in recent years.(Lawrence J Brandt et al., 2012; Eiseman, Silen, Bascom, & Kauvar, 1958; F. Zhang, Luo, Shi, Fan, & Ji, 2012)

Policy and Regulatory Background

In 2013, the Food and Drug Administration (FDA) called for more regulatory oversight and enforcement regarding the use of FMT, pending results of further clinical trial research, except for as a treatment of last resort for recurrent CDI.(*Enforcement Policy Regarding Investigational New Drug*

Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies, 2013; "Fecal Microbiota for Transplantation; Public Workshop," 2013) CDI reporting has been included in the Centers for Medicare and Medicaid Services (CMS) Hospital Acquired Condition (HAC) Reduction Program since January 1, 2014 as part of the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) Healthcare-Associated Infections (HAI) measures, and has been used to calculate hospital-based quality payments since 2017.("Hospital-Acquired Condition (HAC) Reduction Program,") In late 2016, the 21st Century Cures Act passed which includes several sections that pertain to FDA oversight, approval, and availability of treatment options, like FMT, for CDI and other diseases.("21st Century Cures Act," 2016; Zuckerman, Jury, & Silcox, 2015) In 2013, the FDA called for more regulatory oversight and enforcement regarding the use of FMT, pending results of further clinical trial research, except for as a treatment of last resort for recurrent CDI.(*Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies*, 2013; "Fecal Microbiota for Transplantation; Public Workshop," 2013)

STUDY AIMS

The overall goals of this study are to explore the policy and economic implications of expanded use of fecal microbiota transplantation as a treatment option for treatment-resistant diarrhea, using CDI as a use case. The specific aims are:

- **Aim 1:** Review the current state of the literature and findings about CDI and fecal transplants, especially focused on a review of the policies and regulations that pertain to the classification and use of feces.
- **Aim 2:** Identify key issues and barriers influencing gut biome research, potential applications in healthcare innovation, and fecal transplants as a treatment option.

- **Aim 3:** Develop an economic analysis of the expanded use of FMT to treat CDI in the United States, as compared to current standard treatment options.

SIGNIFICANCE OF THE STUDY AND RATIONALE FOR RESEARCH

This research is significant because it represents the intersection of four important and highly complex domains in healthcare and public health– clinical care, policy, research, and patients. Within the domain of clinical care, it touches many challenging topics of high importance including antibiotic use, healthcare associated infections, accessibility of treatment, patient engagement and autonomy,[i] healthcare costs, and supply chain management. Within the policy domain, it touches drug innovation, clinical guidelines, drug development and regulatory processes for getting new drugs to market, quality and safety monitoring of clinical and pharmaceutical interventions, payment and reimbursement policy, and the policy overlap of multiple federal agencies. For advances in research, it covers scientific advances in drug delivery mechanisms, genomics and bioinformatics, and new drug development especially in biologics and biosimilar pharmaceuticals. At the center of the conversation are the patients who are dealing with significant morbidity and mortality, impact to their quality of life, and the accessibility and cost of treatment.

In recent years, there has been recognition from the federal government and leading clinical organizations that both FMT and CDI required more research. In July 2013, the FDA issued Guidance for Industry that stated the FDA would use enforcement discretion[ii] for FMT for CDI "not responding to standard therapies" as long as informed consent was present, and recommended that other uses for FMT fall under the agency's Investigational New Drug (IND) regulations(*Enforcement Policy Regarding*

[i] Patient autonomy is defined as the right of a patient to make decisions about their medical care without their healthcare provider trying to influence or impose on the patient. (Entwistle, Carter, Cribb, & McCaffery, 2010)
[ii] Enforcement discretion refers to the ability of the FDA to judiciously determine whether to pursue enforcement of interim, unclear, or otherwise debated policies and regulations.

Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies, 2013). The National Institutes of Health (NIH) awarded an exploratory grant to develop a regulatory framework for FMT in 2015. In 2016, NIH funded a National Fecal Transplant Registry as a multicenter prospective longitudinal study of the effects of FMT.(Wu, Kelly, & Laine, 2016) (Wu et al., 2016) This dissertation will further inform and contribute to emerging research in the field by analyzing the economic and policy implications of the use of FMT using CDI as a use case.

DISSERTATION ORGANIZATION

This dissertation is organized into five chapters. The first chapter introduces the background, the study aims, and significance of the study and rationale for the research. Chapter 2 summarizes the literature on *c. diff*, fecal transplant, and the policies that govern the use of fecal transplant, as well as the conceptual models that frame the research. Chapter 3 presents the methodology for the study including the aims and methods. Chapter 4 presents the results, and the final chapter describes a discussion of the findings and implications for policies and future research, as well as strengths and limitations of the work. The appendices include the summaries of the articles included in the policy literature review, the Institutional Review Board (IRB)decision letter, key informant interview questions, model schematics, variables and their associated values, and model outputs.

CHAPTER 2. LITERATURE REVIEW

Chapter 2 is divided into three sections: a review of the background literature on *c. diff* and FMT, a systematic review of the literature on the policies and regulations for FMT and human fecal matter, and a review of the practical and conceptual models that ground and inform this research.

I. BACKGROUND LITERATURE

The Microbiome

Bacterial cells on the human body outnumber human cells by between three to ten times, but only make up one to three percent of our body mass; for every gene in the human genome, humans harbor approximately 1,000 bacterial genes. Within the gut alone, there are nearly 100 trillion essential bacteria.(Davenport et al., 2017; Foster & McVey Neufeld, 2013)

Bacteria play significant roles in human bodily processes and functions. Their roles, interactions, profiles, lifecycles, and impact are only beginning to be understood. Rapid and recent advances in clinical genomics have enabled scientists to begin to identify and understand the key roles and interactions that bacteria have in the human body. The Human Genome Project published the first version of the human genome in 2001, and the Human Microbiome Project was established in 2008 "with the mission of generating resources that would enable the comprehensive characterization of the human microbiome and analysis of its role in human health and disease."(International Human Genome Sequencing et al., 2001; "NIH Common Fund Human Microbiome Project (HMP) ", 2008; "An Overview of the Human Genome Project," 2016)

The bacteria colonizing our digestive tracts, or the gut microbiome, make up a complicated and dynamic ecosystem that is implicated in many diseases and important functions. The gut microbiome is even recognized as a distinct organ in the body. The microbiome has been implicated in GI diseases like

Crohn's, ulcerative colitis (UC), and irritable bowel syndrome (IBS), but also include those as varied as asthma, cardiac conditions, obesity, diabetes, Parkinson's, autoimmune functions, and mental health.(Fujimura & Lynch, 2015; Holt et al., 2017; Huang & Boushey, 2015; Knights et al., 2013; Kostic et al., 2014; Michail et al., 2011; Morgan et al., 2012; Rieder et al., 2017; Riiser, 2015; Tang et al., 2017; Tremlett et al., 2017; Wright et al., 2015) The gut is responsible for the production of hormones, neurotransmitters, and their precursors that have been implicated in mood, affect, metabolism, and the immune response.(Martin, Sun, Rogers, & Keating, 2019; E. A. Mayer, K. Tillisch, & A. Gupta, 2015; Mittal et al., 2017) For example, the gut is responsible for 95% of the body's serotonin and more than 50% of the dopamine produced.(Eisenhofer et al., 1997; Martin et al., 2019; Xue et al., 2018) There is increasing evidence that gut microbiota plays a key role in the pathway in the body called the gut-brain axis, in which neurotransmitters travel from the gut to the brain along various pathways including the vagus nerve.(Cryan et al., 2019; Foster & McVey Neufeld, 2013; Emeran A. Mayer, Kirsten Tillisch, & Arpana Gupta, 2015) The vagus nerve acts as the neural "super-highway" in which signals travel between the gut and the brain. There is evidence that the gut-brain axis can be triggered by the microbiome, but there are nearly infinite pathways and mechanisms between the human host and its commensal bacterial colonies that are not yet understood.(Bravo et al., 2011; Forsythe, Bienenstock, & Kunze, 2014)

The gut microbiome is comprised of a highly dynamic, incredibly diverse collection "of bacteria, yeast, fungi, bacteriophages, and other viruses […] as well as protozoa and archaea." At baseline at present in the United States, "the healthy human gut microbiome consists of 8 phyla, 18 families, 23 classes, 38 orders, 59 genera and 109 species. 63 (40%), 32 (20%) and 31 (19.7%) members belongs to *Firmicutes, Actinobacteria* and *Bacteroidetes*, respectively which make up a majority of the bacterial species."(King et al., 2019)

The concentrations of gut bacteria are mutable and change over the lifetime of an individual, over the evolutionary lifetime of our species, and geographically due to cultural, diet, and environmental factors.(Davenport et al., 2017) Among geographical comparisons, the gut biomes of people who have Westernized diets and cultures consist of 15-30% fewer species and consistently lack species that are present in those people with non-Western biomes.(Davenport et al., 2017) The profiles and frequencies of bacteria colonies in the gut biome differ as well; Western biomes consist of more *Bacteroides* while non-Western biomes reflect higher concentrations of *Firmicutes* and *Proteobacteria*.(Davenport et al., 2017) Profiles and frequencies of colonies appear to be reflective of cultural differences in diet from subsistence farming, hunting, and gathering, as well as increased consumption of fiber.(Davenport et al., 2017) Composition changes over the lifespan of an individual; at birth, an infant's microbiome is determined by the route of delivery (i.e., vaginal versus cesarean birth) and the mother's microbiome.(Odamaki et al., 2016) *Actinobacteria* are relatively highest in the infant and early toddler years and decrease after weaning.(Odamaki et al., 2016) *Firmicutes* is the most predominant after weaning and *Proteobacteria* appears highest in concentration in the youngest (i.e., under 4 years) and oldest age groups (i.e., over age 70).(Odamaki et al., 2016)

Clostridioides difficile

Gut dysbiosis can occur when the types and concentrations of bacteria in the gut are disturbed and imbalanced. This can lead to altered, impaired, or poor functioning of the gut. One severe type of gut dysbiosis is from the bacteria *Clostridioides difficile* (formerly *Clostridium difficile*).

Clostridioides difficile (*c. diff*) is an anaerobic Gram-positive spore-forming bacteria that produces toxins in the intestine and causes colitis. Inflammation from *c. diff* is mediated primarily by large toxins, toxin A or toxin B; the toxins induce inflammation of the GI system which leads to diarrhea, tissue inflammation, and necrosis.(W. K. Smits, D. Lyras, D. B. Lacy, M. H. Wilcox, & E. J. Kuijper, 2016)

Symptoms include diarrhea of loose, watery stool multiple times a day and for several days, fever, stomach tenderness and nausea. A unique feature that is a hallmark of *c. diff* is due to the bacteria's production of *p*-cresol, which lends a distinctive scent described as "tar-like or pig-like" in nature.(W. K. Smits et al., 2016)

C. diff was originally identified in 1935 and determined to be the cause of pseudomembranous colitis in 1978.(Wiep Klaas Smits, Dena Lyras, D. Borden Lacy, Mark H. Wilcox, & Ed J. Kuijper, 2016; Jung Hoon Song & You Sun Kim, 2019) In the early 2000s, CDI rapidly spread and increased—first in North America, and then globally—in prevalence, severity, and mortality, thus raising scientific interest in the bacteria, its spread, and treatment.(Wiep Klaas Smits et al., 2016) Surveillance, prevention, and data reporting efforts proliferated to combat the disease. Widespread systematic surveillance started in 2003 after a surge in hospitalizations and mortality attributed to the emergence of two highly pathogenic strains of *c. diff* —PCR ribotype 027 and to a lesser extent, PCR ribotype 078; however CDI epidemics are not limited to these strains.(Wiep Klaas Smits et al., 2016) *C. diff* was reclassified from *Clostridium* to *Clostridioides difficile* in 2016.(The Lancet Infectious, 2019)

Clostridioides difficile infection (CDI) is the most common healthcare associated and antibiotic-associated diarrheal disease, causing an estimated "10-25% of the cases of antibiotic-associated diarrhea, 50-75% of antibiotic-associated colitis, and 90-100% of pseudomembranous colitis."(W. K. Smits et al., 2016; J. H. Song & Y. S. Kim, 2019; Voth & Ballard, 2005) CDI is also the leading cause of gastroenteritis-associated death.(Lessa et al., 2015) CDI causes nearly half a million infections in the U.S. per year and is associated with significant morbidity and mortality both in healthcare facilities and in the community.(Guh et al., 2020; Lessa et al., 2015) Most recent estimates reflect decreasing CDI burden in healthcare facilities since 2011, attributed to a decline in HAI rates. Globally, "the overall rate of healthcare facility onset CDI (HO-CDI) was 2.24 per 1000 admissions per year and 3.54 per 10,000

patient-days per year. Estimated rates for CDI with onset in ICU or internal medicine wards were 11.08 and 10.80 per 1000 admissions per year, respectively. Rates for community-associated CDI (CA-CDI) were lower: 0.55 per 1000 admissions per year."(Balsells et al., 2019) The rates are higher in older adults and in North America.(Balsells et al., 2019) For example, the population-based burden of CDI was "an overall rate of CDI in Massachusetts in 2016 of 132.5 per 100,000 population, with mortality in 2014 of 6.4 per 100,000 population."(Troppy et al., 2019)

CDI can easily reach outbreak or epidemic levels in nursing homes, long term care facilities, and hospitals.(Dubberke & Olsen, 2012; Hunter et al., 2016; Lessa et al., 2015) For example, during an outbreak in a small long-term care facility (LTCF), half of the population screened tested positive for CDI and nearly 40% of surfaces tested were positive for CDI spores.(Endres et al., 2018) In a study of asymptomatic carriers, nearly 15% of LTCF residents were asymptomatic carriers—a number that rose significantly with additional risk factors such as recent hospitalization, antibiotic use, prior infection, or prior facility outbreak.

Approximately 24.2% of CDI acquired in healthcare facilities have hospital onset; the majority of infections are diagnosed and addressed in the community and ancillary facilities, which presents significant additional burden in the healthcare system.(Dubberke & Olsen, 2012; Lessa et al., 2015) While hospital associated CDI has decreased due to an overall decline in HAI, the burden of community-acquired CDI has remained stable. An additional $11,285 per case is attributable to CDI in hospital settings (95% CI: $9118-13,574, in 2012 $USD). CDI costs nearly $5 billion in excess costs annually for acute care facilities, driven by additional length of stay, and has a 30-day mortality rate of almost 10%.(Lessa et al., 2015)

To identify and diagnose CDI, the presence of diarrhea is the most prominent clinical indication. Patients with new and unexplained onset of three or more unformed stools within 24 hours meet the

criteria for CDI testing. (L Clifford McDonald et al., 2018) Once a positive stool toxin test is confirmed, the initial CDI episode is stratified by severity—initial episode, non-severe CDI, initial episode, severe CDI, or initial episode, fulminant CDI. (L Clifford McDonald et al., 2018) Subsequent episodes within one month are considered reoccurrences (i.e., rCDI); severity of disease may change during the progression of the illness, for instance progressing from severe to fulminant during a reoccurrence.

The current treatment for CDI is an antimicrobial approach, using antibiotics in a 10-day course. In the U.S., the recommendation for adults is to treat the initial CDI episode with fidaxomicin or vancomycin for 10-days, with metronidazole as an alternative. In Europe, the recommendation for non-severe CDI is to discontinue antibiotics and use watchful waiting for 48 hours if appropriate; otherwise, metronidazole is the treatment of choice for non-severe CDI, and vancomycin for severe CDI. Canada prioritizes the use of vancomycin for up to 14 days, with metronidazole or fidaxomicin as alternatives. England's and Australia's current guidelines are consistent in recommending the use of vancomycin as treatment for severe CDI, but differ as compared to the U.S. in recommending metronidazole instead of fidaxomicin as a first line therapy.(Trubiano et al., 2016; Mark H Wilcox, Hawkey, Patel, Planche, & Stone, 2013) Fidaxomicin, metronidazole, and vancomycin are usually delivered by mouth/orally via pill (i.e., PO); metronidazone is also available intravenously (IV) for severe and fulminant CDI. Vancomycin is available by PO or alternatively for more severe cases when PO is not tolerated via IV or rectally (PR). For rCDI, vancomycin is also delivered in a "pulse tapered" regimen, a strategy that provides an extended treatment duration over several weeks with tapering doses over time and then continues medication administrations every few days for several more weeks (2-8 weeks) in smaller "pulses."(Murphy, Patatanian, & Gales, 2018)

Prevention and containment are also key to combatting CDI. Prevention efforts must include handwashing with soap and water because as a Gram-positive, spore forming bacterium, alcohol

handwashing does not sufficiently deter *c. diff*.(L Clifford McDonald et al., 2018) Isolation and contact precautions are recommended in inpatient settings for those with suspected or confirmed CDI.(L Clifford McDonald et al., 2018) Lastly, because prior antibiotic usage is a risk factor for CDI, antibiotic stewardship programs are necessary to mitigate CDI risk.(L Clifford McDonald et al., 2018)

While *c. diff* bacteria are not significantly antibiotic resistant, prior antibiotic use is "a dominant risk for the development of CDI."(Bartlett & Perl, 2005; DePestel & Aronoff, 2013; Spigaglia, 2016) While not yet significantly antibiotic resistant, antibiotic resistance and reduced susceptibility to antibiotics has developed for CDI, especially for metronidazole, and has driven epidemiological changes in disease emergence and virulence, especially for recurrent cases.(Spigaglia, 2016; Spigaglia, Mastrantonio, & Barbanti, 2018) In a 2013 CDC report on the threat of antibiotic resistance, *c. diff* was one of three organisms included in the category of threat level of "Urgent" "because of its unique relationship with resistance, antibiotic use, and its high morbidity and mortality."(*Antibiotic resistance threats in the United States, 2013*, 2013) FMT has been explored as a treatment to reduce infection or eliminate colonization from multi-drug resistant organism (MDRO) in lieu of antibiotics; FMT has been shown to have an eradication rate of MDRO of approximately 70% [Range: 37.5% to 87.5%].(Saha, Tariq, Tosh, Pardi, & Khanna, 2019; Tavoukjian, 2019)

Patients report a significant negative impact to their health-related quality of life (HRQoL) from CDI.(Guillemin et al., 2014; Pakyz et al., 2016) Patients experience multiple bouts of diarrhea per day, sometimes 20-30 instances daily. The severity, urgency, and frequency impacts the patient's ability to participate in normal activities of daily living such as attending work, school, or social events and causes emotional, physical, and mental distress.(Guillemin et al., 2014; Pakyz et al., 2016) Patients report feelings of hopelessness, as well as anxiety and distress about the impact of CDI on relationships,

finances, activities of daily living (ADLs), and fears of recurrence in the future.(Guillemin et al., 2014; Pakyz et al., 2016)

Fecal Microbiota Transplant

FMT has been around since the 4th century and is used in veterinary medicine. It has gained popularity in Western medicine for the treatment of gastrointestinal (GI) diseases in recent years.(Lawrence J Brandt et al., 2012; Eiseman et al., 1958; F. Zhang et al., 2012) FMT is the process by which donor stool is mixed with saline to create a slurry and transplanted to the recipient's intestines.(Lawrence J Brandt et al., 2012; Gough et al., 2011) The purpose of an FMT is to replace and replenish the recipient's disrupted or infected gut microbiome in the GI tract with a mix of healthy donor bacteria to cure disease or promote health.

In randomized control trials (RCT), systematic reviews, and meta-analyses, FMT has been shown to be effective as a treatment for rCDI,(Cammarota, Ianiro, & Gasbarrini, 2014; Chapman et al., 2016; Chen et al., 2018; Drekonja et al., 2015; Gough et al., 2011; Hui, Li, Liu, Zhou, & Gao, 2019; Kassam, Lee, Yuan, & Hunt, 2013; Khan, Dirweesh, Khurshid, & Siddiqui, 2018; Y. T. Li, Cai, Wang, Xu, & Fang, 2016; Quraishi et al., 2017; Ramai et al., 2020; Sofi et al., 2013; Yoon, Suh, Kang, & Kim, 2019) ulcerative colitis,(Cao et al., 2018; S. P. Costello et al., 2017; Narula et al., 2017; Shi et al., 2016; Sun et al., 2016; Zhou et al., 2020) IBD,(Chen et al., 2018; R. J. Colman & D. T. Rubin, 2014a, 2014b; Fang, Fu, & Wang, 2018; Imdad et al., 2018; Myneedu, Deoker, Schmulson, & Bashashati, 2019; Paramsothy et al., 2017; Xu et al., 2019) and obesity and metabolic syndrome,(Z. Zhang et al., 2019) among others.(Chinna Meyyappan, Forth, Wallace, & Milev, 2020; Martínez-González & Andreo-Martínez, 2020; Yoon et al., 2019) FMT has been shown to be a very cost-effective treatment for rCDI, as compared to current medication treatment options, and may be less costly and more effective as a treatment.(Baro et al., 2017; Konijeti, Sauk, Shrime, Gupta, & Ananthakrishnan, 2014; L. Lapointe-Shaw et al., 2016; Stalder et

al., 2020; Varier et al., 2015) In RCTs, systematic reviews, and meta-analyses, FMT for CDI has shown an overall efficacy of 92% and an efficacy for severe or recurrent infection of 87%-90%.(Cammarota et al., 2014; Drekonja et al., 2014; Drekonja et al., 2015; Gough et al., 2011; Kassam et al., 2013; Quraishi et al., 2017) FMT can be delivered prepared with either fresh or frozen stool. With regards to preparation methods of FMT, in a comparison of fresh versus frozen stool, both have been shown to be equally effective, while the use of enteric encapsulated FMT capsules show similar effectiveness to fresh and frozen application in the colon but require more doses than coloscopy or nasogastric tube to get to equivalency.(Hirsch et al., 2015; Kao et al., 2017; Lee et al., 2016; Youngster et al., 2016; Youngster et al., 2014)

There are several modalities of delivery of FMT, broadly broken down into two categories: top-down or bottom-up. “Top-down” methods refer to ingesting the sample in the GI system via the mouth to stomach route, either via administration in a nasogastric or duodenal tube or in capsule form. In its earliest forms, FMT was ingested orally by drinking it in a concoction referred by early Chinese practitioners to as “yellow soup” but for obvious “yuck factor” reasons, that modality is no longer preferred.(L. J. Brandt & Aroniadis, 2013; Y. Ma, J. Liu, C. Rhodes, Y. Nie, & F. Zhang, 2017) “Bottom-up” refers to administering the sample to the GI system via the colorectal cavity. Modalities commonly used are colonoscopy and retention enema. Administration via colonoscopy is most effective.(Quraishi et al., 2017; Youngster et al., 2014)

There are several stool donor models for FMT: the “known donor” model in which the donor is an immediate family member or significant other; the “universal donor” model in which a panel of selected but anonymous donors are assembled and all samples are combined to be processed and drawn from; and the “directed donor” model in which the donor is not known to the recipient. The directed donor model has two basic formats. Donors may be sought after and recruited based on traits

such as a certain diet, physique, or health characteristics; the donor and recipient only have contact via the context of obtaining a sample. Other directed donors are anonymous, and the exchange is typically moderated by the FMT provider as an intermediary; for instance, in the Taymount Clinic in the UK and Bermuda, donors provide samples directly to the clinic and are referred to as "Donor 1, 2, etc." Recipients only know that they received samples from an anonymous Donor 123 and/or Donor 456.

The short-term risks and side effects of FMT are similar to a colonoscopy or other GI tract procedures, including intestinal distress and discomfort, bloating, soreness, and possibly nausea or even fever. A systematic review of adverse events from FMT reported a total rate of adverse events of 28.5%, which includes all events from minor stomach discomfort (common) to more severe events (uncommon), such as bowel perforation or death. Severe complications such as bowel perforation are rare but may also occur, especially in fragile or elderly patients. For example, the risk of severe complications from a colonoscopy procedure includes perforation (5.8 per 10,000 colonoscopies), bleeding (2.4 per 1000 colonoscopies), and death (3 per 100,000 colonoscopies).(Kothari et al., 2019) However, these events were attributed to errors in the surgical procedure and not the donor stool.

The long-term consequences of FMT are currently not well understood (as of 2021) and are one facet warranting further research via the FMT National Registry. Long term consequences of FMT could result from alterations to the microbiome that are currently undiscovered or not well tested for or understood, such as change in affect to be more similar to the donor's, weight change resulting in obesity or weight loss, or contracting an illness or condition transmitted by the donor stool or FMT administration. In 2019, several patients contracted drug-resistant *E. coli* from infected stool transmitted via FMT, resulting in two reported cases and one death. The infectious agent had been added to screening protocol in early 2019; however, products in storage were not retroactively retested, resulting in inadvertent transmission. Regarding the current SARS-CoV2 pandemic, the presence of

COVID-19 can be found in stool, signaling that it is possible that it could be transmitted via infected stool and that risk of transmission via stool may be higher than for other tissue transplantations.(Gu, Han, & Wang, 2020; Ianiro et al., 2020; "OpenBiome Updates on COVID-19," 2020; Xiao et al., 2020)

Current pharmaceutical research and development efforts are focused on developing a less invasive, but equally effective administration method, such as the use of freeze-dried sample in an enteric coated capsule, or a proprietary cocktail of probiotics and/or selected bacterial profiles from stool. In the future, other preparations such as probiotic-enhanced or synthetic preparations could be developed and approved for use; for instance, Finch Therapeutics is a biotechnology company that is working to develop cultured and probiotic-enhanced solutions that specifically target disease symptoms, pathways, and causes. They have more than 50 patents and 120 pending patent applications for products across the microbiome field and are developing products to treat CDI, ulcerative colitis, Crohn's, and IBS and Autism Spectrum Disorder with significant GI symptoms. Other research and development competitors in the CDI and FMT fields are Seres Therapeutics and Rebiotix. Seres Therapeutics developed and is testing oral capsules of "consortia of bacteria" specifically selected and curated to address disease pathways, including CDI (SER-109, SER-287, SER-262).("Our Platform," 2020; Vargason & Anselmo, 2018) Rebiotix developed intestinal microbiota suspensions for oral (RBX7455) and enema (RBX2660) delivery to treat rCDI.(2020; Vargason & Anselmo, 2018)

Policy and Regulation

Policy and regulation occur at the federal, state, local, and organizational levels. For policy and regulations related to FMT and CDI, policies originate at the federal and organizational levels. State and local level public health leadership have the authority to enact policy via their state referendum, insurance regulation, or emergency public health powers; such action has been taken for issues such as state Medicaid expansion, legalization of marijuana, and COVID-19 response. However, in the current

use case for the use of FMT for CDI/rCDI, there are no known instances of these types of state-level policy action occurring. Federal level policy and regulation governs production, use, and enforcement of drugs, labs, and healthcare payment policy. At the organizational levels, insurers, hospitals and hospital systems, and professional and specialty societies have policies regarding acceptable treatment of CDI and use of FMT.

Currently in the U.S., FMT is categorized as a drug under the regulatory authority of the FDA. In the U.S., the Food and Drug Administration (FDA) is responsible for licensing, approval, and oversight of drugs which are defined in the Federal Food, Drug, and Cosmetic Act of 1938 as "articles intended for the use in diagnosis, cure, mitigation, treatment, or prevention of disease, and articles (other than foods) that are intended to affect the structure and function of the body of man or other animals." Biologic products are also regulated by the Public Health Service Act which defined biologic products as "a virus, therapeutic serum, toxin, or analogous product application to the prevention, treatment, or cure of a disease or condition in human beings." As such, biologics may be regulated under either or both laws. The FDA's regulatory authority is very broad and the agency has oversight of approximately one trillion dollars' worth of products per year including food, drugs, biologics, medical devices, electronic products that give off radiation including microwaves, cosmetics, veterinary products, and tobacco products. In 2013, the FDA called for more regulatory oversight and enforcement regarding the use of FMT, pending results of further clinical trial research, except as a treatment of last resort for recurrent CDI. In late 2016, the 21st Century Cures Act passed which includes several sections that pertain to FDA oversight, approval, and availability of treatment options, like FMT, for CDI and other diseases.("21st Century Cures Act," 2016; Zuckerman et al., 2015) ("21st Century Cures Act," 2016; Zuckerman et al., 2015)

The Centers for Disease Control and Prevention's (CDC) mission is to "fight disease and supports communities and citizens to do the same" which includes "detecting and responding to emerging health threats."("CDC Mission, Role and Pledge,") As such, CDC collects and maintains surveillance data on existing and emerging health threats. Active community-based surveillance for CDI began in 2009 via the CDC's Emerging Infections Program (EIP) Healthcare-Associated Infections Community Interface (HAIC). The CDC National Healthcare Safety Network (NHSN) Healthcare-Associated Infections (HAI) Facility-wide Inpatient Hospital-onset CDI Measure was developed by the CDC and first received National Quality Forum (NQF) endorsement in 2012.[iii]

CDI reporting has been included in the Center for Medicare and Medicaid Services (CMS) Hospital Acquired Condition (HAC) Reduction Program since January 1, 2014 as part of the CDC NHSN HAI measures, and has been used to calculate hospital-based quality payments since 2017. Foundational to their mission, CMS has a responsibility to pay for health insurance provided via Medicare and Medicaid; their interest in CDI is predicated on a health insurance payment strategy that accounts for quality reporting and payment to incentivize the delivery of quality care.

Last, there are many general regulations, laws, and provisions that touch many of the related processes pertaining to CDI and use of FMT. For example, regulation and oversight of laboratory and diagnostic testing on humans are the responsibility of the FDA, CDC, and CMS under Clinical Laboratory Improvement Amendments (CLIA) with each federal agency responsible for separate aspects of the regulation and oversight processes. Regarding general patient protections, patient health information is protected under Health Insurance Portability and Accountability Act (HIPAA) of 1996 via the Office of Civil Rights, and when appropriate the Department of Justice for criminal violations; patient consent for

[iii] NQF was created in 1999 during the Clinton administration to promote and ensure patient protections and healthcare quality through measurement and public reporting; it is the only consensus-based healthcare organization defined by the Office of Management and Budget.

participating in testing medical treatments falls under Office for Human Research Protections (OHRP) enforcement and oversight of Institutional Review Board (IRB) ethical review of research practices. Good Manufacturing Practice (GMP) compliance regulations are enforced by the FDA to ensure safe manufacturing practices and production of many consumer goods. There are many complex and overlapping regulatory and policy components that touch the many facets of disease and treatment lifecycle processes and pathways to ensure appropriate safety and overall public health; the distal and proximal issues surrounding CDI and FMT cross the breadth of this policy landscape.

Table 1 displays a list and description of relevant legislation, policies, and regulations at the federal, state, and organizational level that apply to CDI or FMT as a treatment that were identified during the literature review.

Table 1. Relevant CDI and FMT Legislation, Policy, and Regulation

Agency or Stakeholder	**Legislation, Policy, &/or Regulation**
	Federal level
FDA	• Good Manufacturing Compliance (GMP) compliance • Investigational New Drug (IND) Oversight • New drug approval • Lab test approval • Lab monitoring and enforcement (CLIA) • Adverse event reporting • Post-market surveillance
CMS	• Lab accreditation (CLIA) • Quality reporting and payment programs, such as HAC Reduction
NIH Clinical Trial Registration and Submissions	• ClinicalTrials.gov
OHRP Medical Ethics	• Institutional Review Board (IRB) • Informed Consent
21st Century Cures Act (2016)	Excerpt and Summary of Relevant Subsections. (Zuckerman et al., 2015) **Subtitle B--Qualification and Use of Drug Development Tools** • (Sec. 2021) The FDA must establish a process to qualify drug development tools (methods, materials, or measures that aid drug development and regulatory review) as reliable for use in supporting approval or investigational use of a drug. • (Sec. 2022) The sponsor of a drug for a serious condition may request that the FDA agree to an accelerated approval development plan. The plan must include the design of the drug study. **Subtitle D--Modern Trial Design and Evidence Development**

	• (Sec. 2061) The FDA must issue guidance that addresses using alternative statistical methods in clinical trials and in the development and review of drugs. • (Sec. 2062) To support approval of a drug for a new indication, the FDA must evaluate the use of evidence from clinical experience (in place of evidence from clinical trials) and establish a streamlined data review program. **Subtitle E--Expediting Patient Access** • (Sec. 2082) Manufacturers and distributors of investigational drugs for serious conditions must publish their policies on expanded access (also known as "compassionate use"). **Subtitle G--Antibiotic Drug Development** • (Sec. 2121) At the request of the sponsor of an antibacterial or antifungal drug for treatment of a serious infection, the FDA may agree on a process for developing data to support approval of the drug for use in a limited population of patients. • HHS must monitor the use of antibacterial and antifungal drugs and resistance to these drugs.
State-level Examples	
State Medical Boards	• Maryland Board of Physicians • Maryland Board of Nursing • Maryland Pharmacy Board
Local and/or Organizational-level Examples	
Institutional policy for infection prevention	• University of California San Francisco Health Hospital Epidemiology and Infection Prevention Policy Manual, Section 4: Hospital-Wide Policies and Procedures("University of California San Francisco Health Hospital Epidemiology and Infection Prevention Policy Manual," 2021) • University of North Carolina Healthcare Infection Control Policies("UNC Healthcare Infection Control Policies," 2019)
Institutional policy on infection surveillance and reporting	• University of California San Francisco Health Hospital Epidemiology and Infection Prevention Policy Manual, Section 8.2: Infection Surveillance("UCSF Health Hospital Epidemiology and Infection Prevention Policy Manual," 2019) • Johns Hopkins Hospital Epidemiology and Infection Control("Hospital Epidemiology and Infection Control,")
Institutional policy on applying for and use of IND	• Fairview Health Services IND Policy("Investigational Drug Policy," 2018) • Duke University Expanded Access Policy("Expanded Access," 2020) • Johns Hopkins IND Policy("Office of Human Subjects Research - Institutional Review Board," 2020)
Hospital policy on use of stool bank for procurement	• University of Michigan uses the "known donor" model as well as OpenBiome.("Stool Transplant Provides Bowel Disorder Relief,") • Henry Ford Health System Supply Chain Management Policies("Supply Chain Policies," 2021)
Hospital policy on adverse event reporting	• University of Toledo Medical Center Policy on Sentinel Events, Never Events, and Adverse Events("Sentinel Events Adverse Events and Never Events," 2020) • Tenet Health Event Reporting Policy Model/Template Document("Event Reporting," 2018)
Insurance policy on approval and payment for treatment with FMT	• Blue Cross Blue Shield (BCBS) Massachusetts Medical Policy Example("Medical Policy: Fecal Microbiota Transplantation," 2020)

	• EmblemHealth Medical Policy Example("Fecal Microbiota Transplant (FMT) For Recurrent Clostridium Difficile Infection," 2020) • Medicare HCPCS Billing Code G0455[iv]
Stool bank policies on safety monitoring and surveillance	• OpenBiome Quality and Safety Program(*OpenBiome Quality and Safety Program*, 2020) • OpenBiome Monitoring and Traceability Guide("OpenBiome Monitoring & Traceability Guide," 2020) • OpenBiome Adverse Event Reporting Form("Adverse Event Reporting Online Form," 2020)
Specialty society guidance on FMT	• "Fecal microbiota transplantation: a practical update for the infectious disease specialist" (2013)(Moore, Rodriguez, & Bakken, 2014) • Infectious Diseases Society of America (IDSA) Guidance on FMT("Emerging Issues: Fecal Microbiota Transplantation," 2020)
Specialty society guidance on CDI	• Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) Guidelines(L Clifford McDonald et al., 2018) • European Society of Clinical Microbiology and Infectious Diseases Guidelines(Debast, Bauer, & Kuijper, 2014) • Association of Medical Microbiology and Infectious Disease Canada Guidelines(Loo et al., 2018) • Australasian Society of Infectious Diseases Guidelines(Trubiano et al., 2016) • Public Health England Guidelines(Mark H Wilcox et al., 2013)

Regarding state level policy, the licensing of medical professionals falls within the jurisdiction of the state medical boards. While not specific to CDI or FMT, if a provider were negligent in diagnosis or treatment or provided treatment beyond what is generally acceptable, safe, and approved, complaints about the practitioner can be made to the state board and the provider's medical license could be suspended or revoked by the state licensing board. For example, if a provider offered FMT therapy without adhering to current clinical guidelines, they could be at risk of losing their license and could be liable for any patient harm caused. It is in the best interest of providers to adhere to treatment standards and policies and endorsed guidelines of practice to safeguard their professional reputation and livelihood. However, there is demonstrated variation by state in the amounts of disciplinary action and/or malpractice claims permissive by the medical boards and courts, stemming largely from variation in state regulations, procedures, and disciplinary action policies.

[iv] HCPCS Billing Code G0455 has been in effect since 1/1/2013 and is for "preparation with instillation of fecal microbiota by any method, including assessment of donor specimen."

At the local level, operationally clinical practice is determined by local and organizational norms, policies, procedures, and workflows. In this use case, the local organizations are generally hospitals and other healthcare institutions, patients, insurers, and healthcare providers. Hospitals and healthcare institutions have policies that guide infection prevention, diagnosis and treatment, surveillance and reporting, and adverse event reporting. Hospitals make decisions, implicitly or explicitly, that inform their policies and practices, such as if they engage in research and have an IRB, if they support Investigational New Drug (IND) applications which can be cumbersome, expensive, and time-consuming, and purchasing decisions like lab or procedure equipment or participation in a stool bank. Providers often use evidence-based practice recommendations as a basis to inform treatment decisions, and typically, insurance providers limit coverage determinations based on evidence-based guidelines and recommendations. A national panel of experts determines clinical practice guidelines and recommendations after reviewing the scientific literature and consensus-building discussions. Results are disseminated via peer reviewed journals and conferences, as well as through local chapters and word of mouth. Lastly, safety and quality monitoring and reporting is not consistent across healthcare settings; hospitals and other healthcare institutions have voluntary adverse event reporting systems, but their use and efficacy are driven by local safety culture.(Miller et al., 2019; Mitchell, Schuster, Smith, Pronovost, & Wu, 2016) Labs and producers, such as drug and medical device manufacturers, are also responsible for quality and safety monitoring and surveillance, but again, practices can vary widely in their rigor and scope.

II. Systematic Review: Policy and Regulation of FMT and Human Fecal Matter Classification

Purpose

Prevention of *c. diff* and implementation of treatment options are increasingly well studied at the clinical level. Cost effectiveness and comparative effectiveness analyses of FMT support that FMT is an efficacious and economical treatment option.(Cammarota et al., 2014; Ruben J Colman & David T Rubin, 2014; Drekonja et al., 2015; Gough et al., 2011; Kassam et al., 2013; Konijeti et al., 2014; L. Lapointe-Shaw et al., 2016; Shi et al., 2016; Varier et al., 2015) However, far fewer studies have focused on the policy, regulatory, and economic considerations of the classification of human fecal matter and use of FMT.

The number of articles in PubMed pertaining to FMT has grown rapidly since 2000; only 54 articles in total using the terms fecal transplant were published prior to 2000. From 2013 to 2015, the number of publications on fecal transplant doubled annually and from 2014 to 2018, publications have increased four-fold from approximately 100 per year to 400 per year. However, the downstream impact of treatments targeting the gut biome including the use of FMT have not been extensively studied in the policy literature. In 2021, PubMed searches for “fecal transplant” and “policy” resulted in approximately 50 results in total (double the amount as the same search in 2019), as compared to the nearly 3,500 for fecal transplant alone, and of the results, only a handful discussed policy considerations. A similar trend is observed for “fecal transplant” and “health economics.”

Search Terms

The following search terms were used in nine unique search combinations: fecal microbiota transplantation, fecal microbiota transplant, and fecal transplant; and policy, legislation, regulation, and economics. The search terms were identified using MeSH terminology; “Fecal Microbiota

Transplantation" is the highest-level MeSH term specific to FMT and was introduced in 2016 and "Policy" is also the highest-level MeSH term available and was introduced in 2011. "Government regulation" falls under the larger category of "social control, formal" along with legislation. Health economics is one of several search terms that fall under the larger entry of "Health Care Economics and Organizations," a MeSH term added in 1998.

Sources

PubMed, PsycINFO, CINAHL Plus, Embase, the Cochrane Review, and Web of Science were searched through January 2021. Qualitative and quantitative studies, as well as reviews, commentary, and editorials that include mention of policy in conjunction with the use of FMT were included; U.S.-focused articles as well as those from other countries were included. Clinical trials were excluded.

Outcomes of Interest

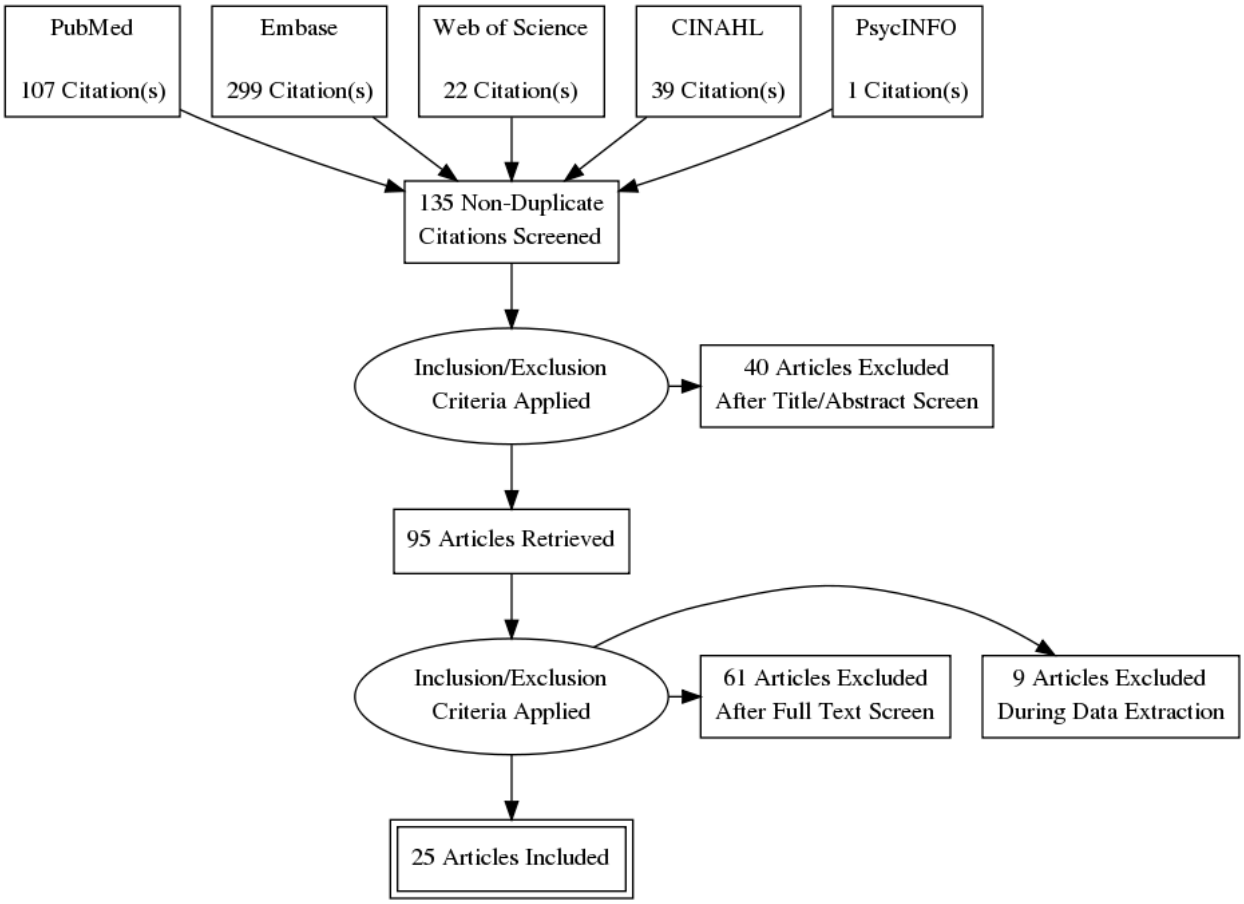
The primary outcome of interest was articles discussing policy and regulatory considerations for FMT and/or stool including results from the U.S. and internationally. Included in the analysis was if stool is regulated as tissue, drug, biologic drug, or some other classification; donor selection policy; preparation and administration of FMT; and policies regarding the clinical indication for treatment. Other topics of interest were economic reviews and analyses for healthcare systems in which economic analyses inform coverage and payment policies, payment policy, the predominant donor model, clinical guidelines used, and the regulatory oversight body. Abstracts were screened by a single reviewer and full articles identified for inclusion were abstracted by the primary reviewer.

Article Results

In total, 450 articles were identified from the search engines. Of those, 135 non-duplicate citations were screened, resulting in 40 articles excluded during the abstract and title screen and 95 retrieved for full

text review. Of those, 61 were excluded in full text review and nine were excluded during data review and extraction. In total, twenty-five articles met criteria for inclusion. Figure 1 displays the number of articles reviewed by source and the final number of articles reviewed in the scan.

Figure 1. Flow Diagram and Results of FMT Policy Literature Review



Description of Articles

Included studies

Most articles identified were original research, typically describing a proposed framework for classifying stool and FMT in a regulatory setting as well as reviewing the history and pros and cons regarding current policies about FMT and the classification of stool. There are ten included. The second most common article type was editorial or commentary discussing operational concerns pertaining to FMT and stool regulations. There are nine editorial and commentary articles included. The remaining six articles are review articles that provide a comprehensive summary and review of relevant topics and evidence to date, including one regulatory review and opinion article in a law journal. The included articles are listed in Table 2 and summarized in Appendix A.

Table 2. Included Studies

Authors	**Title**
Costello SP, Bryant RV	Faecal microbiota transplantation in Australia: bogged down in regulatory uncertainty
Costello SP, Van Der Poorten D, Andrews JM	Fecal microbiota transplantation for recurrent Clostridium difficile infection: When regulatory affairs do not keep pace with evidence-based medicine
Edelstein C, Daw JR, Kassam Z	Seeking safe stool: Canada needs a universal donor model
Edelstein CA, Kassam Z, Daw J, Smith MB, Kelly CR	The regulation of fecal microbiota for transplantation: An international perspective for policy and public health
Hoffmann D, Palumbo F, Ravel J, Roghmann MC, Rowthorn V, Von Rosenvinge E	Improving regulation of microbiota transplants
Hoffmann DE, Palumbo FB, Ravel J, Rowthorn V, von Rosenvinge E	A proposed definition of microbiota transplantation for regulatory purposes
Hvas CL, Baunwall SMD, Erikstrup C	Faecal microbiota transplantation: A life-saving therapy challenged by commercial claims for exclusivity
Jørgensen SMD, Hvas CL, Dahlerup JF, et al	Banking feces: a new frontier for public blood banks?
Keller JJ, Ooijevaar RE, Hvas CL, et al	A standardised model for stool banking for faecal microbiota transplantation: a consensus report from a multidisciplinary UEG working group
Keller JJ, Vehreschild MJGT, Hvas CL, et al	Donated stool for faecal microbiota transplantation is not a drug, but guidance and regulation are needed
Khoruts A, Hoffmann DE, Palumbo FB, Rothstein MA, Knoppers BM	The Impact of Regulatory Policies on the Future of Fecal Microbiota Transplantation
Labuschaigne M, Slabbert M, Budree S, Hoosien E, Brink A, Blockman M	The ethicolegal framework relevant to human faecal microbiota transplants in South Africa: Part 2

Lagier JC	Faecal microbiota transplantation: From practice to legislation before considering industrialization
Lin TC, Hung YP, Ko WC, Ruan JW	Fecal microbiota transplantation for Clostridium difficile infection in Taiwan: Establishment and implementation
Ma Y, Liu J, Rhodes C, Nie Y, Zhang F	Ethical Issues in Fecal Microbiota Transplantation in Practice
Megerlin F, Fouassier E	Faecal microbiota transplantation in France: What applicable law?
Mullish BH, Williams HRT	Obstacles to establishing an NHS faecal transplant programme
Ossorio PN, Zhou Y	FMT and Microbial Medical Products: Generating High-Quality Evidence through Good Governance
Sachs RE, Edelstein CA	Ensuring the safe and effective FDA regulation of fecal microbiota transplantation
Salman S, Vardatsikos G, Avard D, Palmour N, Dewar K, Zawati MH	FMT Happens: Regulating Fecal Microbiota Therapy in Canada; What You Need to Know
Scheeler A, Hoffmann DE, Rothstein MA, Knoppers BM	Where Stool is a Drug: International Approaches to Regulating the use of Fecal Microbiota for Transplantation
Smith M, Kassam Z, Edelstein C, Burgess J, Alm E	OpenBiome remains open to serve the medical community
Terveer EM, van Beurden YH, Goorhuis A, et al	How to: Establish and run a stool bank
Verbeke F, Janssens Y, Wynendaele E, De Spiegeleer B	Faecal microbiota transplantation: a regulatory hurdle?
Vyas D, Aekka A, Vyas A	Fecal transplant policy and legislation

Excluded studies

The most common reason for exclusion was because the article did not include the outcome of interest. In the title and abstract review, of 135 articles, 40 were excluded as not being relevant. During the second review, 61 more articles were excluded, and of those, nearly all were excluded due to not including the outcome of interest (n=51); the remaining articles excluded were not primary studies (n=10). During the final review, nine articles were excluded—all because they did not include the outcome of interest.

Policies and Policy Domains Identified

FMT is regulated via policy addressing the following domains: classification of human stool, availability and selection of the donor (Donor Model), preparation, the clinical indication for use of FMT, how treatment is paid for, stool bank governance and oversight, and the convening bodies that provide

clinical guidelines and regulatory oversight. The policy and policy domains identified in the literature review informed the development of the FMT process diagram outlined and discussed in Chapter 4. Section II. A comparison of policies by country or geographic region is listed in Table 3.

Table 3. Policy Comparison by Country or Geographic Region

Region	**Classification of FMT**	**Donor Model**	**Preparation**	**Clinical Indication**	**Clinical Guidelines**	**Oversight**	**Payment**
USA	Drug	Known donor or universal donor via stool bank	Stool bank or Physician	rCDI after third round of antibiotics. All other uses require an IND and participation in a clinical trial.	Yes, ACG	National (FDA)	Insurance coverage with co-payment/co-insurance when clinically indicated
Canada	Drug (created new designation as a new biologic drug)	Directed Donor	Physician	CDI resistant to conventional therapy (generally after the 2nd round of failed antibiotics)	Yes	National (Health Canada)	If public insurance, for CDI/rCDI. With private or no insurance, out of pocket (OOP).
United Kingdom	Medicinal product	Directed Donor	EU-Good Manufacturing Practices (GMP)	rCDI or if paying out of pocket, any/none.	Yes, National Institute for Health and Care Excellence (NICE)	National	If public insurance, for CDI/rCDI. With private insurance, OOP.
Australia	Drug (although not listed in the country's drug registry)	Directed Donor	Physician	None Stated	Yes	National	If public insurance, for CDI/rCDI. With private insurance, OOP.
European Countries in the European Union (EU)	Exempt	Generally, Directed Donor	Physician or Pharmacist	rCDI after second round of antibiotics and UC	Yes, EU Gastrointestinal (EUG) Working Group with guidance from European Society for Clinical Microbiology and Infectious	European Tissue and Cells Directive (EUTCD)	If public insurance, for CDI/rCDI. Costs to patient not discussed.

					Diseases (ESCMID)		
Denmark	Exempt	Hospital operated stool bank	Hospital staff (e.g., Physician or Pharmacist)	rCDI	EUG and ESCMID	EUTCD	Free in public hospitals.
Netherlands	Exempt	Public Stool Bank	Stool bank staff and Physician	rCDI, Pilot study for IBS, Clinical trial for MDRO bacteria	EUG and ESCMID	EUTCD	Stool is purchased directly from the stool bank. Costs to patient not discussed.
Taiwan	None stated	FMT program (affiliated with health systems/ hospitals)	FMT team members	rCDI and UC	Yes, Taiwan Microbiota Consortium and Taiwan FMT Expert Consensus	National, Taiwan Microbiota Consortium and Taiwan FMT Expert Consensus	None stated.
Hong Kong	None stated	Known Donor	Stool bank staff and Physician	CDI, rCDI, Clinical trial for IBS, IBD and MDRO bacteria	None stated	None stated	None stated. Likely OOP
South Africa	Not currently classified	Directed Donor	Researchers (e.g., Physician)	rCDI	South African Gastroenterology Society	National, under the South African National Health Act 61 of 2003	N/A. Currently used for research purposes only. Costs to patient not discussed.

Other (e.g., medical tourism sites)	Varies, but often falls under “the practice of medicine”	Varies (e.g., universal donor, "premium" donor, known donor)	Physician	Any/None	No	No	OOP

In late 2019, an article “Where Stool Is a Drug: International Approaches to regulating the Use of Fecal Microbiota for Transplantation” was published in the *Journal of Law, Medicine, and Ethics* by author Alexandra Scheeler that succinctly summarizes the existing policies and regulations in the U.S. and abroad that cover stool and the use of FMT. The article details the regulatory classification of stool in the fifty most populous countries and countries that are determined to have advanced economies as determined by the International Monetary Fund, resulting in a summary table of 75 countries and three Special Administrative Regions; this analysis is far more inclusive and robust than what was determined from a systematic literature review and provides the most seminal policy and regulatory review on the classification of stool and its use in FMT to date. In addition, in the discussion of regulations and policy in the U.S., the author identifies four critical approaches to the “regulatory paradigm” regarding the classification of stool, including one point made by the FDA that had not been previously identified in any of the literature.

In brief, these four approaches of the regulatory paradigm are: biologic drugs which are highly regulated and have restricted use; human cell and tissue based products which have process focused regulation; medicinal products where authorities claim oversight but there are highly variable requirements and access; and “the practice of medicine” which has decision making delegated to providers, oversight delegated to the providers’ supervisory institution, and unpredictable safety and access at the patient level. An important discussion point for U.S.-focused regulatory efforts is that the FDA’s Tissue Reference Group argues that stool cannot meet the legal definition to be classified as a

human cell and tissue-based product because the active ingredients in stool are bacterial in origin. In addition, based on the legal definition in the U.S., human cell and tissue-based products are not "secreted or extracted human products, such as milk, collagen, or cell factors"[v] as human secretions/extractions fall under a separate legal definition and regulatory framework in the U.S.(A. Scheeler, 2019) In contrast, the European Union's European Tissue and Cells Directive (EUTCD) has determined that while the active ingredient in stool is bacteria, and thus non-human in origin, that stool is arguably and legally defined as a human product, and not a drug.(*Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718), Meeting of the Competent Authorities for Tissues and Cells.*, 2014; Hvas, Baunwall, & Erikstrup, 2020)

Conclusion

There is not one satisfactory answer for a comprehensive, robust, and flexible regulatory framework for stool and FMT. Some countries have taken an operational approach and chosen to focus their energy on the regulation and oversight of stool banks; others are early enough in the process that they lack a regulatory or legal decision on stool and FMT categorization. Regardless of the regulatory determination, a flexible and extensible framework that prioritizes scientific rigor, access, and patient safety will be needed for stool, FMT and in the future for other innovations.

[v] 21 CFR 1271.3 (2001)

III. CONCEPTUAL MODELS

Two conceptual models are presented to explore the policy and economic implications of expanded use of fecal microbiota transplantation as a treatment option for treatment-resistant diarrhea, using CDI as a use case. First, Kingdon's Policy streams and window model will be used to examine the alignment of regulatory and payment options to effective treatment options for an urgent healthcare need.(Kingdon & Thurber, 1984) Next, the framework described by Rogers regarding the diffusion of innovations describes the mechanisms and factors that influence how the interest in and use of FMT has and will spread.(Rogers, 2010)

A. Kingdon's Policy Streams and Window Conceptual Model

For policy innovations, the theoretical framework to examine the alignment of regulatory and payment options for effective treatment options for an urgent healthcare need is Kingdon's policy window. Kingdon originally described the policy window conceptual framework in 1984. The model describes the problems, policy environment, stakeholders, and how policy ideas move from inception to implementation. The model is depicted as a window with convergent and divergent "streams" of problems and corresponding solutions, politics, and policies for solutions flowing towards the window. The opening of the policy window represents the time point at which the streams converge, and the opportunity to make or implement policy change is created. Participants include, but are not limited to, government and elected officials, advocates and organized political forces, academics, researchers, think tanks, media, and the public.

Participants

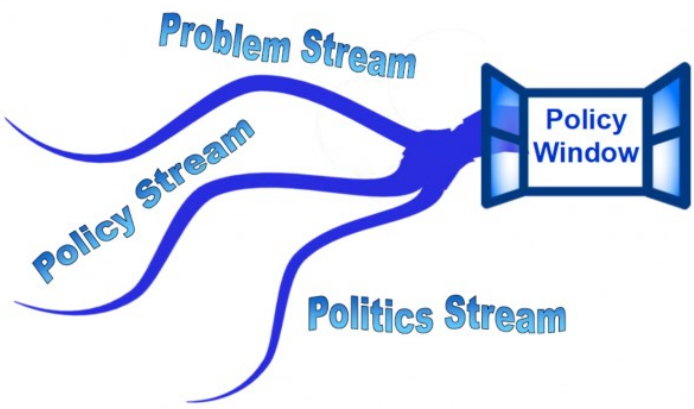
The participants in the model are involved in each of the streams but are divided into two categories: those in and outside of government. Within government, the participants are the

Administration, civil servants, and those elected officials on Capitol Hill or the state government; outside of government, the participants are academics, researchers, and consultants; the media and the public; and interest groups including professionals like medical and healthcare providers or manufacturers. All participants are important but play different roles in how they affect policy agendas versus alternatives and differ in the resources available to them.

The Streams

The model includes three streams—the problem stream, the policy stream, and the politics stream. Each stream is independent but converge when a policy window opens. The Kingdon Policy Streams and Window Model is shown in Figure 2.(R. D. Thakur, 2014).

Figure 2. Kingdon's Policy Streams and Window Model



Problem Stream

The problem stream represents the myriad of problems that are present, in formation, or fading at any given time. Problems can be any issue—transportation, healthcare costs, infrastructure, energy sources, etc.—that may come to the attention of decision makers. Indicators are monitored by decision makers and are used "to assess the magnitude of the problem and to become aware of changes in the problem."(Kingdon, p 91) Common indicators include budget allocation and spending, prominent

discussion among decision makers, public opinion, media coverage, and key performance indicators specific to the issue. Changes in an indicator can also constitute a problem, as a steady indicator is preferable to one in flux as it signals change that may need to be addressed by the decision maker.

Problems may coalesce around focusing incidents that elevate attention to the problem, such as a crisis or the attention of a decision maker with personal experience with the problem. Focusing incidents are not the sole catalyst for the problem stream though; focusing incidents need accompanying factors. For instance, one focusing incident may not be enough to elevate the problem within the problem stream, but several occurring within a short time frame or receiving more media attention than usual would. Similarly, focusing incidents may be accompanied by a crisis or reach a certain threshold that raises the problem into focus and attention within the problem stream. Problems may fade from prominence because it has been truly solved or there is a narrative that decision makers can use to say that the problem is solved, such as legislation passed, or action taken.

Policy Stream

The policy stream represents the short list of viable policy options that have been developed and agreed upon by the policy community. The policy stream represents the evolution of ideas and solutions that originated in the "policy primordial soup" and have evolved and continued their lifecycle as they advance up the stream. The policy stream represents the available policy proposals flowing towards convergence at the end of the stream. The policy stream includes the community of specialists who are responsible for policy generation and development. These policy communities can include researchers, academics, policy and budget analysts, staffers, and special interest groups. The policy community also includes participants that Kingdon describes as "policy entrepreneurs" who advocate for and advance a specific policy proposal or idea in the stream. Policy entrepreneurs are named as such because they are willing to invest significant resources with the hope of future return. As well-known

and vocal advocates for specific policy, they are key to taking advantage of the policy window when it opens and coupling solutions to problems. A current example of a policy entrepreneur is Shannon Watts and her work on gun policy reform.

To describe the originations of the policy stream, Kingdon uses the analogy of the "policy primordial soup," similar to the primordial soup in which biologists believe life on Earth originated; in the "policy primordial soup," policy ideas swirl, intermingle, and evolve until it eventually coalesce enough to make its way in the policy stream, and eventually the world, when the conditions are amenable. Criteria for the policy to advance from the soup into the stream include feasibility, acceptability and aligning with values, barriers to implementation, available alternatives, and what the emerging consensus and tipping point is among participants; these criteria echo the criteria for an innovation that are described in the Rogers' model for Diffusion of Innovation in Chapter 2 Section III.B.

The policies and regulations that are applicable *c. diff* and FMT are identified and discussed in the literature review (see Chapter 2 Section II) and a list of policies and regulations are provided in Table 1.

Politics Stream

The politics stream refers to the national mood, social movements, government and elected officials, organized political forces, and the government. The government is heavily influenced by turnover of key personnel and issues of jurisdiction and locus of control. The politics stream functions via consensus building through the national mood, social movements, and organized political forces which spread to government and elected officials, and then the bandwagon effect or a "tipping point" occurs. The bandwagon effect or tipping point is when a certain threshold is reached where enough people have adopted the idea such that its further spread is self-sustaining on its own momentum. This

concept is also described by Rogers in his conceptual model of the diffusion of innovations and is described in more detail in Chapter 2 Section III.B.

Policy Window and Joining Streams

A policy window is the opportunity to act; the policy window only opens for a short duration and is actionable when the streams are joined—a problem is recognized, a solution is available from the policy community, and political change is feasible, and the political constraints are not severe. Windows may open because of an alteration in the streams or from events external to the stream. Predictable events that open windows include budget cycles, renewals, reports and addresses, while unpredictable events include random convergence of streams, crisis, or spillover from another topic.

Proposed solutions are constantly swirling and being revised in the policy stream. When a window opens, the policy community, especially the policy entrepreneurs, push their solutions. Coupling occurs when a proposed solution is attached to a problem, rather than the problem seeking for a solution in the stream. When a solution could be applicable to many problems and a window opens, advocates are forced to adapt their policy solution to the problem at hand or wait until another window opens.

Kingdon notes that "none of the streams are sufficient by themselves to place an item firmly on the decision agenda" and that the "probability of an item rising on the decision agenda is dramatically increased if all three streams—problems, policies, and politics—are joined."(Kingdon, p 178) Decisions are dependent on resource commitment by participants and are made by bargaining, majority coalition building, and building consensus until the tipping point is reached.

Once the policy window opens, it does not stay open for long. The opening is reliant on convergence and timing, and outcomes can be unpredictable. Reasons for the window closing include that politicians feel they have addressed the problem, there is failure to get action, events pass,

personnel may change, or there is not an available and feasible alternative solution. Overload can also happen. When overload happens, the problem can fall in on its own weight; however, if participants are willing to invest more resources, they can solve all the problems or solve a manageable subset of problems. "The more participants are willing to commit their resources, the more problems can be resolved, and the more alternatives would be dispatched."(Kingdon, p 177)

B. Rogers' Diffusion of Innovations Conceptual Model

The Rogers' Diffusion of Innovation model is a theoretical framework that can be used to describe the uptake of FMT as an innovative treatment option and its diffusion in the marketplace. The model, originally described in 1962, has been updated in four subsequent editions. Rogers states in the preface of the 4th edition that "[n]o other field of behavior science research represents more effort by more scholars in more disciplines in more nations."(Rogers, 2010) As such, the model has been extensively applied to healthcare.(Barnett, Vasileiou, Djemil, Brooks, & Young, 2011; Berwick, 2003; Cain & Mittman, 2002; Dearing, 2009; Fitzgerald, Ferlie, & Hawkins, 2003; Greenhalgh et al., 2005; Sanson-Fisher, 2004; R. Thakur, Hsu, & Fontenot, 2012)

Elements of Diffusion of Innovation

There are four main elements in the diffusion of innovations: the innovation, communication channels, time, and a social system. Rogers defined an innovation as "an idea, practice, or object that is perceived as new by an individual or other unit of adoption," whereas the diffusion of the innovation is defined as "the process by which an innovation is communicated through certain channels over time among the members of a social system. It is a special type of communication, in that the messages are concerned with new ideas. […] Diffusion is a kind of social change, defined as the process by which alteration occurs in the structure and function of a social system."(Rogers, 2010)

Rogers discusses that characteristics of the innovation may be paired together to help aid or speed diffusion. These pairings are referred to as “technology clusters” in which “one or more distinguishable elements” of the technology innovation “are perceived as being closely interrelated.”(Rogers, p 15) An example in the microbiome research is the use of probiotic enhanced FMT; the innovations of FMT and probiotic therapy are coupled in this application. However, they are distinct innovations. Similarly, the classification of stool in a newly created regulatory category that accounts for the biodynamic nature, as well as the heterogeneity of the product could also be conceived as a “technology cluster.” Advances in both the policy and regulatory framework, as well as with the production of the product are interrelated, but distinct. With clusters, the diffusions of the innovations are highly interdependent.

The process of diffusion is described as four steps: the innovation; the individual or unit that adopts the innovation; another party that does not have experience with the innovation; and finally, the communication channel between the two parties. Communication channels are the link by which content and ideas are exchanged and the innovation is spread. Communication channels include information exchange such as mass media (one-to-many relationship) and interpersonal communication (one-to-one relationship). “More effective communication occurs when two or more individuals are homophilous. […] One of the most distinctive problems in the diffusion of innovations is that the participants are usually quite heterophilous.”(Rogers, p19)

Rate of Adoption

The rate of adoption of the innovation is “the relative speed with which an innovation is adopted” by the population and is represented by an S-shaped curve that shows the percent uptake across the population.(Rogers, p 22) The innovation’s rate of adoption is a function of the perceived

attributes of the innovation, type of innovation decision, communication channels, the nature of the social system, and the extent of the change agents' promotion efforts.

As a function of time and the innovation, Rogers also describes the concepts of reaching a threshold and critical mass. "A threshold is the number of other individuals who must engage in an activity before a given individual will join that activity."(Rogers, p 320) The concept of critical mass comes from nuclear physics when a nuclear core goes critical; "the critical mass occurs at the point at which enough individuals have adopted an innovation so that the innovation's further rate of adoption becomes self-sustaining."(Rogers, p 313) Of note, in assessing the threshold, the individual is the unit of analysis whereas in critical mass, it is a system-level measurement. The concepts are important to this research as they are measures of how gut biome research and the use of FMT in clinical practice have advanced, and represent the time at which research and practice, respectively, become widespread and commonly accepted.

There are several strategies for getting to critical mass. The first strategy is to "target top officials in an organization's hierarchy for initial adoption."(Rogers, p 326) This accelerates the rate of adoption by focusing efforts on the nature of the organization's official social system, or organizational leadership, as well as the organization's communication channels, as the adoption would be announced and communicated through official and unofficial organizational channels. The next strategy is to "shape individual's perceptions of innovation." In healthcare and in business today, the shaping of perception is often accomplished through publications and thought pieces in journals, which also uses commonly accepted communication channels, and through presentations, networking, and presence at industry conferences. Businesses may also use social media "influencers"—individuals who use their social media platform and communication channels to promote an idea or product to their audience. Another

strategy to get to critical mass is to introduce the innovation to a group that will adopt it, such as having a new drug added to a large health plan's drug formulary.

The last strategy Rogers mentions is using incentives for early adoption of the innovation. Incentives in medicine and healthcare, especially when used by pharmaceuticals or in exchange for physician referrals, may be considered problematic; policies have been passed to prohibit direct incentives to providers known as "kickbacks" (e.g., Stark Law[vi] and the Anti-Kickback Statute[vii]) and to increase transparency (e.g., Sunshine Act[viii]). Alternatively, indirect incentives such as recognition awards and financial grants for pioneering work, such as the Nobel Prize or the MacArthur Fellows Program, the first cut at market share, and additional revenue from innovative approaches are widely espoused in healthcare. Quality measurement programs that directly reward high achievement and/or performance on quality measures with payment incentives or publicity and exposure (e.g. public reporting on Hospital Compare) are widely employed in the US healthcare system.

The Social System

The social system is an important component of the diffusion of innovation because it offers the network of individuals and/or organizations by which the innovation is spread and adopted. Social norms are the established and acceptable range of behaviors in a social system. Social norms play an important function in diffusion. First, understanding how the innovation is communicated and how it fits into social norms (or not) is important. For example, if people do not regularly discuss their gastrointestinal health with their medical providers, then the topic of FMT is unlikely to arise and diffusion of the idea cannot occur; however if—in the privacy of their homes and with the anonymity of the internet—patients regularly engage on online patient forums, including discussions about their gut

[vi] 42 U.S.C. § 1395nn
[vii] 42 U.S.C. § 1320a-7b(b)
[viii] 42 U.S.C. § 1320a–7h

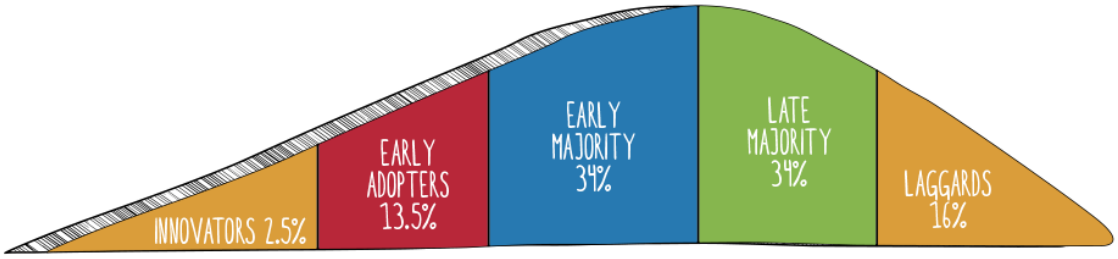
health and activity, the topic of FMT is much more likely to be discussed. The range of options available in a social system is highly variable and depends greatly on what is considered within the acceptable social norms.

Opinion leaders and change agents within a social system are the catalysts for the diffusion and adoption of innovations. By functioning at the center of interpersonal communication networks in a social system, they serve as an important node in the network and can efficiently communicate widely within the social system, thus serving as a catalyst to speed diffusion and adoption of innovations.

Spectrum of Adopters

Rogers described a spectrum of adopters within the population: Innovators, Early Adopters, Early Majority, Late Majority, and Laggards (see Figure 3 (Hanlon, 2013)). Diffusion occurs when adoption reaches above a certain threshold—16%—or the "tipping point" at which adoption accelerates; 16% is equal to the percentages of the first two categories of adopters—innovators (2.5%) and early adopters (13.5%). The term "tipping point" refers to the point in time when diffusion has reached critical mass, is self-propelled throughout the population, and does not rely on stakeholder effort and resources to fuel adoption.

Figure 3: Roger's Diffusion of Innovation Model Spectrum of Adopters



Organizational Innovativeness

Organizational innovativeness is particularly important in healthcare because healthcare decisions are made more and more at the larger organizational level. Health insurance options are

largely determined by employers. Benefits coverage is determined by insurers. Delivery of care is determined within a health system. Physician practice is determined by the physician practice organization. Evidence based treatment guidelines are determined by a professional organization. Even an individual's health and life expectancy are largely attributable to the community where they reside.(LeCounte & Swain, 2017; Thornton et al., 2016) Thus, organizational innovativeness is critical to the adoption and diffusion of health-related innovations.

Organizational innovativeness is determined by individual leader characteristics, internal characteristics of the organizational structure, and external characteristics of the organization. An organization that is highly innovative must have individual leaders with positive attitude to change. Within the organizational structure, the innovative organization is characterized as large, highly complex and interconnected, decentralized, with a lack of formalization, but with some organizational slack to allow time and space for innovation to occur. Externally, the organization shows system openness to allow permeability into the organization.

Innovation Process in an Organization

There are five stages of the innovation process in an organization—agenda setting, matching, redefining/restructuring, clarifying, and routinizing. The innovation process in an organization is important to consider in this research for two reasons. First, the processes of agenda setting, matching, and to some extent redefining and restructuring are currently ongoing in organizations and at the federal policy level regarding FMT use. Second, the process Rogers describes is similar to Kingdon's concept of streams discussed in Chapter 2 Section III.A.

Consequences

There are three types of consequences for an innovation-decision in a social system: desirable versus undesirable; direct versus indirect; and anticipated versus unanticipated. These consequences can impact individuals or groups within the social system, can occur immediately or more gradually over time, and/or can be changes that are recognized and intended or not. Desirable consequences refer to changes in the social system caused by the innovation that increase functionality, rather than those that increase dysfunction (i.e., unintended consequences). Direct consequences are defined as those changes caused by the innovation that occur immediately and proximally to the innovation in the social system, versus indirect consequences which occur more distally or later in time. Anticipated versus unanticipated consequences refer to those changes caused within the social system that are intended and recognized, or vice versa.

CHAPTER 3. METHODS

Scientific advances in FMT clinical research are outpacing current policies and regulations governing its use to treat *c. diff* and other diseases caused by gut dysbiosis. This research used a systematic literature review and key informant interviews to identify key issues and barriers in gut biome research, discuss the potential for fecal microbiota transplantation (FMT) as a treatment option, identify other innovative treatments for gut-mediated illness, and to evaluate the policies and procedures regulating and impacting the use of FMT. An economic model was developed to explore the cost-effectiveness of expanded use of FMT to treat clostridium difficile infection (CDI) in the United States, as compared to current standard treatment options.

Ethics Statement

This study was not determined to be human subjects research and was exempted from review by the Johns Hopkins University School of Medicine Institutional Review Board; the decision letter is included in Appendix B for reference.

I. Key Informant Interviews

Purpose

Key informant interviews were conducted with the purpose of identifying important and emerging themes in the field as well as informing model development. As FMT is an emerging therapy, many key informants have personal considerations, opinions, and experiences that have introduced them or compelled them into this area. However, the key informant interviews were focused on discovering the themes and trends that shape the research and practice landscape, and not exploring personal experiences with *c. diff* and FMT.

In qualitative research, the number of interviews is critically important to achieve a sufficient sample size to ensure robust, reliable, and valid results, as well as saturation around key themes. Best practices for number of interviews varies by discipline but is generally accepted to be no less than fifteen. Given that within the course of this research, only four (4) people participated in interviews, the quality of the results cannot be considered to be sufficiently evidence-based, reliable, and valid to draw conclusions from; thus, the interview content is used for information and guidance only and does not serve to support any statistically valid conclusions in this research.

Identification

Key informants are defined as professionals, patients, or other experts/leaders in the fields of policy and/or practice related to fecal transplant, *c. diff* and other diseases of the gut, microbiome, and healthcare practice, economics and policy. Key informants were identified using a convenience sample and snowball methodology; key informants were identified from the list of stakeholders who touched various components of the FMT process map (shown in Figure 8).

Outreach and Recruitment

Outreach was conducted via email; potential interviewees were emailed with an introduction and brief description of the student researcher and the dissertation research. Informed consent was obtained by providing oral consent in the interview. Scheduling of an interview is implied consent to be interviewed but oral consent was obtained for interviewing, recording, and/or identifying participants. Subjects were asked for oral rather than signed consent as interviews were conducted primarily via phone.

Data Collection

The semi-structured interview protocol was developed using the approaches outlined by the UCLA Center for Health Policy Research, the Agency for Healthcare Research and Quality (AHRQ), and the NIH.(*Anthropological Approaches: Uncovering Unexpected Insights About the Implementation and Outcomes of Patient-Centered Medical Home Models*, 2003; P, 2006; "Qualitative Methods in Health Research: Opportunities and Considerations In Application and Review ", 1999) The AHRQ interview resources are specific to another topic (i.e., patient centered medical home), but includes generalizable basics of approaches to qualitative interviewing and data capture, and thus was considered appropriate for use in this research. One individual was responsible for outreach and recruitment, scheduling, interviewing, and recording. The interview protocol is included in Appendix C. Although these interviews were not considered human subjects research, oral consent was still obtained prior to the interview; the oral consent script is included as Appendix D. Interviews were recorded, and notes were transcribed following the interview.

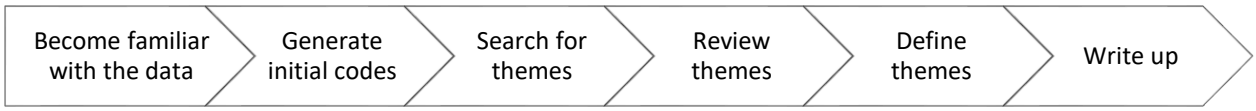
The names and identities of participants are not intended to be anonymous or confidential, unless consent to allow name or identifying information is denied. The research gathered in this study falls within the domain of information that is offered in the spirit of open source information in the public domain in order to promote and advance potentially lifesaving procedures and knowledge sharing.

Thematic Analysis and Identification

Thematic analysis was conducted using the six-step process for qualitative thematic analysis identified by Braun and Clark in 2006, and practically described step-by-step in a 2017 paper by McGuire and Delahunt.(Braun & Clarke, 2006; Maguire & Delahunt, 2017) The six steps are described in Figure 4.

While these steps were originally identified and described for thematic analysis in psychology, they are flexible and generalizable to other domains that are using qualitative research.

Figure 4. Six Steps for Thematic Analysis



Using the methods described by Bree and Gallagher, Microsoft Excel was used to analyze the qualitative data for key themes pertaining to gut biome research, applications in healthcare innovation, and fecal transplants as a treatment option.(Bree & Gallagher, 2016) To analyze qualitative data in Excel, all of the comments and responses from the interviews were input into one column. Additional columns with the corresponding question number and respondent type were also included. After searching and reviewing the raw comments, thematic domains were identified. The themes were reviewed by the primary researcher to make sure they were consistent with the overall tone and content of the interviews and reviewed to identify if there were any outliers. All comments were coded. Then, themes were consolidated and summarized and are presented in the Results section (see Chapter 4, Section I).

II. Health Economic Model

Purpose

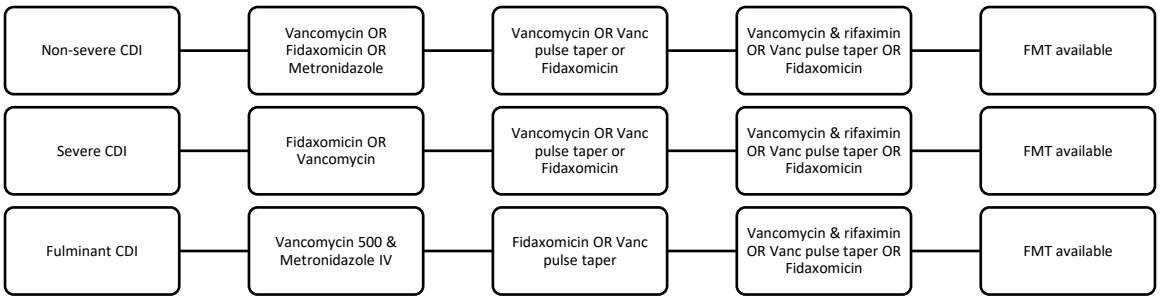
The purpose of the model is to test the cost-effectiveness of expanded use of FMT to treat CDI in the United States, as compared to current standard treatment options. In the model, we use a decision tree to test using FMT to treat rCDI under the status quo, as compared to using it earlier in treatment. We also test the cost effectiveness of FMT as compared to prevailing medications—vancomycin, fidaxomicin, and metronidazole—currently in use for the treatment of CDI and rCDI.

Model Design

The model was developed and analyzed in TreeAge Pro 2020, R2 (Williamstown, MA).("TreeAge Pro, Healthcare Module," 2018) To develop the model framework, clinical pathways and practice guidelines for CDI were reviewed, as were several cost effectiveness studies of FMT.(Baro et al., 2017; "Clinical Pathway for Clostridium difficile Infection," 2013; Lauren Lapointe-Shaw et al., 2016; L Clifford McDonald et al., 2018; Michel, Flores, Mull, & Tsou, 2019) The model framework utilizes decision tree logic in the analyses. The model frameworks are depicted in simplified form in

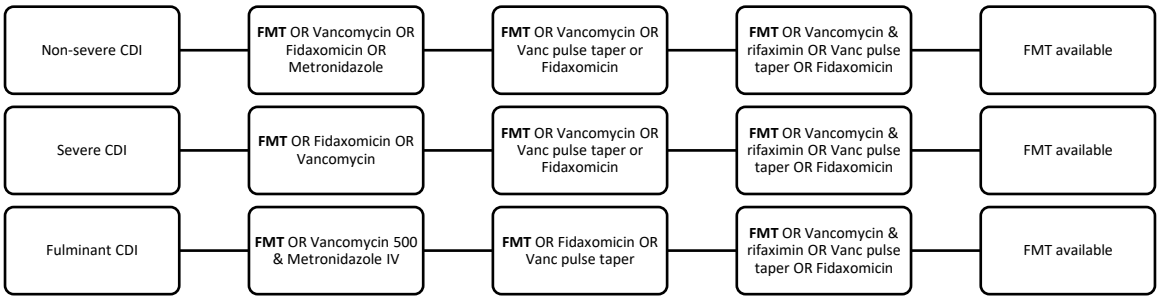
Figure 5 and Figure 6 and are displayed in full in Appendices F and G. The sequences of treatment options are from the IDSA clinical practice recommendations and are explained in detail in Table 9.

Figure 5. Simplified Model Framework—Status Quo Scenario



The simplified model framework for the status quo scenario (Figure 5) provides a representation of the decision tree model for each stage of initial CDI, followed by three episodes of rCDI. The outcomes in the decision tree at each node were defined as one of the following: recovery from CDI/rCDI resulting in terminating node (i.e., return to health), Death resulting in a terminal node, or reoccurrence of CDI (i.e., rCDI) and a probabilistic selection of a subsequent treatment option. In the status quo scenario, FMT is available after the third rCDI. The FMT decision tree results in a probabilistic selection of FMT via pill, enema, or colonoscopy, at which point the nodes terminate with either death or a return to health.

Figure 6. Simplified Model Framework—Alternative Scenario



The simplified model framework for the alternative scenario (Figure 6) shows a representation of the decision tree model for each stage of initial CDI, followed by three episodes of rCDI. The outcomes in the decision tree at each node were defined as one of the following: recovery from CDI/rCDI resulting in terminating node (i.e., return to health), Death resulting in a terminal node, or reoccurrence of CDI (i.e., rCDI) and a probabilistic selection of a subsequent treatment option. In the alternative scenario, FMT is available as a first line therapy for the initial CDI, as well as for each following rCDI. As in the previous scenario, the FMT decision tree results in a probabilistic selection of FMT via pill, enema, or colonoscopy, at which point the nodes terminate with either a return to health or death, or continue on with a reoccurrence of rCDI. In the alternative scenario, FMT is only permitted as a treatment option to be used three sequential times before terminating the node with either a return to health or death.

Model Input Variables

Model input variables were identified during the literature review and are explained and displayed in each section below. Value ranges were estimated from the 95% confidence intervals, standard deviations, or ±10% of the point estimate. All input variables and values are defined and included in Appendix E. Table 19.

Disease Prevalence

Disease prevalence estimates were obtained from the epidemiologic literature on CDI and rCDI. CDI exhibits variability by geography and strain/ribotype as well as changes in the epidemiology of the disease over time. As such, the most recent estimates of prevalence and frequency of CDI were used. For all disease stages, a total of four episodes of CDI/rCDI were assumed before the decision tree branch was terminated; said another way, we assumed the maximum possible episodes of CDI in the model is the initial episode of CDI and three reoccurrences. Prevalence estimates and the incidence rate of death are shown in Table 4.

Table 4. Disease Prevalence and Incidence of Death

Variable	Definition	Value (Range)	Source
Initial non-severe CDI	Prevalence of patients with initial, non-severe CDI diagnosis	51%±10%	Calculated as 1-(severe + fulminant CDI prevalence)
Initial Severe CDI	Prevalence of patients with initial, severe CDI	47%±10%	(Sheitoyan-Pesant et al., 2016)
Fulminant CDI	Prevalence of patients with fulminant CDI	2%±10%	(Sartelli et al., 2019)
Death	Probability of death from CDI	8.6%±10%	(Hensgens, Goorhuis, Dekkers, van Benthem, & Kuijper, 2013)

Costs

Prescription drug costs were estimated from data in the CMS Drug Dashboard. Cost per claim from 2018 was used for each of the medications recommended for use in the treatment of CDI and rCDI.

Part D prescription drug data was used, as it is the most complete set of prescription drug cost data. The Part D cost per claim data represents the average cost per claim pooled across multiple modalities and doses of the drug; one claim was assumed to be the cost equivalent of one round of treatment. The data represents costs in calendar year 2018 and thus was inflated to estimated 2020 dollars using annual prescription drug inflation rate for all insurance types (i.e., public and private insurance).

FMT costs were estimated using the published prices for FMT solution and capsules from OpenBiome.(""How much will an FMT cost me?"," 2020) OpenBiome's estimate for laboratory screening of stool was used as the upper bound of an estimate for FMT via enema if screening was conducted independently.(""How much will an FMT cost me?"," 2020) The estimated cost of a colonoscopy was obtained from an AHRQ Healthcare Cost and Utilization Project statistical brief on healthcare utilization and cost.(Russo, Elixhauser, Steiner, & Wier, 2006) The estimate was from 2007 and was inflated to 2020 dollars using an annual hospital cost inflation rate for all insurance types (i.e., public and private insurance).(*NHE Projections, 2019-2028, Table 6 Hospital Care Expenditures*, 2020) Cost estimates are presented in Table 5.

Table 5. Drug Cost Estimates

Cost Variable	**Definition**	**Value (Range)**	**Source**
Fidaxomicin	Cost per claim of fidaxomicin	$3943 ±10%	(*Medicare Part D Drug Spending Dashboard & Data*, 2019)
FMT colonoscopy	Cost of FMT via colonoscopy	$5349 ±10%	(A. Khoruts, Hoffmann, & Palumbo, 2019) Cost of the colonoscopy was calculated from the cost of an OpenBiome sample and estimated colonoscopy procedure cost from AHRQ 2007 data.(""How much will an FMT cost me?"," 2020; Russo et al., 2006)
FMT enema	Cost of FMT via enema	$1600 ($100-$3500)	UL is cost estimate for screening from

			OpenBiome, 2020(""How much will an FMT cost me?"," 2020)
FMT pill	Cost of FMT capsule per dose	$2050 ($2050-$6150)	OpenBiome, 2020(""How much will an FMT cost me?"," 2020)
Metronidazole IV	Cost per claim of metronidazole IV	$30 ±10%	(*Medicare Part D Drug Spending Dashboard & Data*, 2019)
Metronidazole PO	Cost per claim of metronidazole PO	$46 ($25-$454)	(*Medicare Part D Drug Spending Dashboard & Data*, 2019)
Rifaximin	Cost per claim of rifaximin	$2156 ±10%	(*Medicare Part D Drug Spending Dashboard & Data*, 2019)
Vancomycin	Cost per claim of vancomycin	$305 ($1-$8219)	(*Medicare Part D Drug Spending Dashboard & Data*, 2019)

Externalities and Adverse Events

In previous models, externalities, like antibiotic resistance, are not included, as it is not explicitly included in the overall costs or side effects of CDI and rCDI treatment. This model attempted to include the cost of excess antibiotic exposure and resulting antibiotic resistance by using estimates from the literature of additional cost per antibiotic course by drug class at risk for antibiotic resistance.(Shrestha et al., 2018) The incremental costs are shown in Table 6 and were added to the base costs of the drugs used in the model. Rifaximin is in its own drug class, and there was not available data for the incremental cost of antibiotic resistance for this drug.

Table 6. Incremental Costs of Antibiotic Resistance per Treatment Course

	Glycopeptides (Vancomycin)	**Narrow Spectrum Antibiotics (Metronidazole)**	**Macrolide (Fidaxomicin)**
Cost per course	$8.70	$18.60	$1.70

With regards to adverse events due to FMT, adverse events of concern include colectomy in fulminant CDI, complications requiring hospitalization with ICU stay, adverse events during colonoscopy such as bowel perforation, and potential infection from an unknown pathogen. Potential side effects such as stomach discomfort and bloating are considered relatively minor, but may also occur. Although in perception, risk of adverse events seems to be high on the list of why not to pursue FMT, the actual

incidence of adverse events, calculated as a weighted average of the risks of adverse events, is very low (0.058%). See Table 7**Error! Reference source not found.** for the calculation of the incidence of adverse events from FMT. These adverse events were identified and considered, but were ultimately excluded from the model due to their very low overall risk (0.058%) and thus their minimal contribution to the overall model outcomes.

Table 7. Incidence of Adverse Events from FMT

Adverse Event	**Events (n)**	**Population**	**Rate**	**Weight**	**Source**
Risk of Colectomy	31	1146	2.70%	0.34%	(Shivashankar et al., 2013)
Risk of CDI complications requiring ICU stay	306	1146	26.70%	0.35%	(Shivashankar et al., 2013)
Risk of complications from colonoscopy	228	277,434	0.082%	83.67%	(Arora, Mannalithara, Singh, Gerson, & Triadafilopoulos, 2009)
Risk of infection from unknown pathogen	6	53,000	0.0113%	15.98%	FDA("Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Events Likely Due to Transmission of Pathogenic Organisms," 2020) Open Biome (for denominator data)("Open Biome Impact," 2020)
TOTAL WEIGHTED AVERAGE	540	331,580	0.058%		*Calculated as the sum of the adverse events, weighted by population size of the study, divided by the total population included*

Efficacy

The efficacy of each CDI treatment option was identified from the evidence summarized in the treatment guidelines.(L. C. McDonald et al., 2018) The efficacy of FMT without the prior use of antibiotics was estimated to be lower than the values reported in the literature. This is because it has been hypothesized that FMT is effective after the gut biome has been completely erased through the prior use of antibiotics, and then the new donor biome is able to establish and flourish. A threshold analysis was conducted during the sensitivity analysis to determine at what efficacy FMT would no longer be a feasible treatment option for a first round of therapy. Efficacy estimates are presented in

Table 8.

Table 8. Efficacy Estimates

Efficacy Variable	Definition	Value (Range)	Source
Fidaxomicin	Efficacy of fidaxomicin at 10 days	88% (0-88%)	IDSA(L. C. McDonald et al., 2018)
FMT colonoscopy	Efficacy of FMT via colonoscopy	87% (80%-99.99%)	(A. Scheeler, 2019)
FMT enema	Efficacy of FMT via enema	62.1% (0-62.1%)	(A. Scheeler, 2019) (Lee et al., 2016)
FMT pill	Efficacy of FMT via pill	73.3% (68%-91%)	(A. Scheeler, 2019) (Youngster et al., 2016; Youngster et al., 2014) Hirsh 2015(Hirsch et al., 2015) Used average of primary cure rates
Metronidazole	Efficacy of metronidazole at 10 days	75% (0-75%)	IDSA(L. C. McDonald et al., 2018)
Rifaximin	Efficacy of rifaximin	85% (0-85%)	IDSA(L. C. McDonald et al., 2018)
Vancomycin	Efficacy of vancomycin at 10 days	58.5% (31%-85%)	Point estimate: midpoint between UL & LL LL: (van Nood et al., 2013) UL: IDSA(L. C. McDonald et al., 2018)
Vancomycin pulse taper	Efficacy of extended vancomycin pulse taper	61% ±10%	(Murphy et al., 2018)

Sequence of Treatment Options

For the status quo scenario, IDSA-recommended treatment guidelines were used to construct the sequences of treatment options for each severity of disease.(L. C. McDonald et al., 2018) The treatment options are shown in Table 9.

Table 9. IDSA Clinical Practice Guidelines for Treatment of CDI and rCDI

Disease Stage	Recommendation
Initial episode, non-severe	• VAN 125 mg given 4 times daily for 10 days, OR • FDX 200 mg given twice daily for 10 days • Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days
Initial episode, severe	• VAN, 125 mg 4 times per day by mouth for 10 days, OR

	• FDX 200 mg given twice daily for 10 days
Initial episode, fulminant	• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present
First reoccurrence (2nd episode of CDI)	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR • Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (e.g., 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR • FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode
Second or subsequent recurrence (≥3 episodes of CDI)	• VAN in a tapered and pulsed regimen, OR • VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR • FDX 200 mg given twice daily for 10 days, OR • Fecal microbiota transplantation

Treatment via FMT was assumed to be 5-day treatment durations to account for prep, procedure, and recovery time. Vancomycin pulse taper was assumed to be the median number of days recommended in the treatment guidelines, 60 days.(L. C. McDonald et al., 2018) Vancomycin and rifaximin, used for rCDI, was assumed to be a 30-day duration, per the treatment guidelines.(L. C. McDonald et al., 2018) Fidaxomicin, standard vancomycin treatment, and metronidazole were assumed to be 10-day duration, per the treatment guidelines.(L. C. McDonald et al., 2018) In the status quo scenario, no treatment options for FMT were used until the third occurrence of rCDI, per the current treatment guidelines.(L. C. McDonald et al., 2018) Total treatment duration was calculated as the sum of all treatment options represented in the decision tree. The duration of treatment for each sequence is shown in Appendix E. Tables 21-23.

Outcome Measure

The outcome for the cost effectiveness analysis was cost ($USD) per quality adjusted life year (QALY), expressed as the incremental cost effectiveness ratio (ICER). An ICER is calculated as the difference in costs between interventions divided by the difference in health outcome (i.e., effectiveness) of the interventions. The ICER calculation is shown below.

Equation 1. ICER Calculation

$$ICER = \frac{\Delta \text{ Total } Cost}{\Delta \ Health \ Outcome} = \frac{Total \ Cost_a - \ Total \ Cost_b}{QALY_a - \ QALY_b}$$

Quality adjusted life years (QALY) is a measure of the value of health outcomes that combines the quantity and quality of life lived. QALYs are a function of time and utility during disease and treatment. In the multiplicative approach to QALYs, QALY is expressed as the product of the utility value and time (i.e., 1 QALY=1 utility weight x 1 year). An alternative QALY calculation can account for discounting future life years, the duration of illness, and life expectancy and quality of life by age. The QALY calculation is shown below.

Equation 2. Quality Adjusted Life Years

$$\boldsymbol{QALY = D \times \frac{(1 - e^{-rL})}{r}}$$

Where *D* is disability weight (also expressed as 1-*Q*=*D*, where *Q* is health-related quality of life weight), *L* is the duration of the illness expressed in years, *r* is the discount rate (*r*=3%), and *e* is Napier's mathematical constant (*e*=2.71828).

Disability weights are a metric to grade the severity of illness on a scale from 0 to 1, where the disability weight of death is 1 and perfect health is 0. Disability weights from the Institute for Health Metrics and Evaluation (IHME) global burden of disease are most commonly used to define DALYs. *Q* represents the health-related quality of life weight attached to the relevant year of life when the disease begins. Utility weights are a metric to grade the severity of the disease state on a scale from 0 to 1, where the utility weight of death is 0 and perfect health is 1 (i.e., the inverse of disability weights). Utility weights are considered an analogous alternative to HRQoL weights (*Q*) but do not have the arithmetic inverse relationship to disability weights (1-*Q*=*D*).

Disability adjusted life years (DALYs) were considered as the outcome measure since DALYs averted due to alternative treatments or earlier intervention conceptually makes sense in the context of CDI and the use of FMT. Disability adjusted life years (DALYs) is a societal-level metric of disability that is defined as the sum of the life years lost (YLL) and years lost to disability (YLD). The DALY calculation is simpler (DALY= YLL + YLD), but must be completed separately for each age range and illness duration combination examined, which increases the complexity in assessing the model outcome; of note, there is a useful DALY calculator available online that was explored for the DALY calculations for CDI, using the IHME disability weights for diarrheal disease. However, QALYs were ultimately chosen because it is comparable to other cost effectiveness studies whereas DALYs averted is less commonly used.

A CDI-specific utility weight was identified in the literature; it was determined via qualitative survey data among a cohort with CDI from the United Kingdom.(M. H. Wilcox et al., 2017) The point estimate was used to represent the utility weight of severe CDI (0.42); utility weights for mild-moderate and severe complicated/fulminant disease states were estimated using the standard deviation (0.42 (SD ±0.29)).(M. H. Wilcox et al., 2017) Recurrent episodes of CDI used the utility weight associated with the severe disease state (0.42) with the mild-moderate and fulminant states as the lower and upper bounds, respectively (0.42 (SD ±0.29)).(M. H. Wilcox et al., 2017) All estimates were rounded to the nearest tenths place. In the model, it is assumed that the utility weights are constant, regardless of age, and stable throughout the duration of illness, both for simplicity's sake and because more granular estimates do not exist. Utility weights for the associated disease states are shown in Table 10.

Table 10. Utility Weights for CDI

Disease State	Utility Weight
Severe, complicated/fulminant CDI, Initial episode	0.1
Severe, complicated/fulminant CDI, Recovered (1 year)	0.7
Severe, not complicated CDI, Initial episode	0.4
Severe, not complicated CDI, Recovered (1 year)	0.8
Mild-moderate CDI, Initial episode	0.7
Mild-moderate CDI, Recovered (1 year)	0.9
Perfect Health	1
Death	0

To calculate QALYs, the Complex Number approach, rather than the multiplicative approach, was used. In the multiplicative approach, QALYs are the value of years of life lived multiplied by utility value where 1 year of life x 1 utility value=1 QALY, whereas the Complex Number approach takes into account the different data types of time and function and the calculation captures the dimensional nature of the measure with a proportional ratio of time and function units. The corresponding value of QALYs on the utility scale (i.e., 0-1) when time is held constant (i.e., *t*=1 year) were used to calculate the CDI-specific QALYs for the disease states and duration of illness in the model (i.e., QALY x duration of

illness for each respective utility weight), shown in Table 11. The QALY conversion table that was used is included in the appendix for reference (see Appendix E. Table 20).

Using this approach, 1 day is the equivalent to 0.0024 QALYs for mild-moderate CDI, 0.0021 for severe CDI, and 0.0019 for fulminant and severe CDI with complications. To calculate the QALYs in the model, the duration of treatment and severity of disease were considered, and the QALY outcomes are a product of total treatment duration in days and the associated QALYs per day.

Table 11. QALYs over time by CDI stage

Duration of treatment (days)	Severe- fulminant CDI	Severe, not complicated CDI	Mild-moderate CDI
	Utility Weight of 0.1	Utility Weight of 0.4	Utility Weight of 0.7
5	0.0097	0.0104	0.0118
10	0.0195	0.0209	0.0236
15	0.0292	0.0313	0.0355
20	0.0389	0.0417	0.0473
25	0.0487	0.0522	0.0591
30	0.0584	0.0626	0.0709
35	0.0681	0.0730	0.0828
50	0.0973	0.1043	0.1182
70	0.1363	0.1461	0.1655
75	0.1460	0.1565	0.1773
80	0.1557	0.1669	0.1892
85	0.1655	0.1774	0.2010
100	0.1947	0.2087	0.2365
110	0.2142	0.2295	0.2601
130	0.2531	0.2713	0.3074

Total treatment duration was calculated as the sum of all treatment options in the decision tree (described in Table 9), and the corresponding QALY was assigned based on the total treatment time and severity of disease (as shown in Table 11s 21-23 in Appendix E). The QALYs accrued at each terminal node in the decision tree as payoffs are normalized to a 1-year time horizon (i.e., 365 days). Death has a QALY payoff of 0. QALYs accrued are a function of QALYs calculated for each treatment duration and severity multiplied by the duration normalized to 1 year, less the time lost to treatment, normalized to 1 year.

Equation 3. QALY Payoff Calculation

$$QALY\ Payoff\ for\ each\ node = \left(QALY\ at\ t_x \times \left(\frac{t_x}{365}\right)\right) + \left(\frac{365 - t_x)\ \times 1}{365}\right)$$

Where t_x represents the number of days in the duration of treatment.

Analysis

A cost effectiveness analysis was conducted with a willingness to pay (WTP) of $100,000 per QALY under two scenarios: the base case was defined as status quo treatment options with the use of FMT after the third episode of rCDI and the alternative in which FMT is a treatment option as a first- and second-line therapy. A willingness to pay of $100,000 is assumed based on the World Health Organization's (WHO) recommendation to use one to three times the average Gross Domestic Product (GDP) per capita as a cost effectiveness threshold per QALY gained; $100,000 is a historically and commonly used cost effectiveness threshold for the U.S.(Cameron, Ubels, & Norström, 2018; Marseille, Larson, Kazi, Kahn, & Rosen, 2015; Neumann, Cohen, & Weinstein, 2014; Ubel, Hirth, Chernew, & Fendrick, 2003) Unless otherwise specified, variables and parameters were assumed to be independent.

Sensitivity Analysis

One-way sensitivity analyses for cost, effectiveness, and net monetary benefit (NMB) was conducted on those variables determined to be driving the model outcome, with their ranges defined by 95% confidence intervals from the literature, upper and lower limits of the variable values as identified from the literature, or ±10% of the point estimate, as available.

CHAPTER 4. RESULTS

The results section is divided into three parts. First the results of the key informant interviews are presented. Next the CDI and FMT process diagram that was constructed during the course of this research is presented. Last, the results of the economic model analyses are presented.

I. Key Informant Interviews

Interviews

Four (4) interviews from June to December 2016 were conducted via phone. The respondents were a GI physician who treated *c. diff* and used FMT with a research interest in probiotics therapy, a nurse who worked on an adult surgical intensive care unit where CDI and rCDI were common, a patient advocate and recipient of a lifesaving FMT, and a staff from a public stool bank. In addition to the four interviews conducted, initial outreach to an additional six (6) informants was attempted, but received no response. Thus, the response rate for an interview request was 40% (4/10=40%).

Among the four respondents, 123 unique comments were generated in the interviews. The majority of comments (n=55, 45%) were contributed by the patient advocate, followed by the stool bank representative (n=30, 24%). The breakdown of the number of comments by respondent is shown in Table 12.

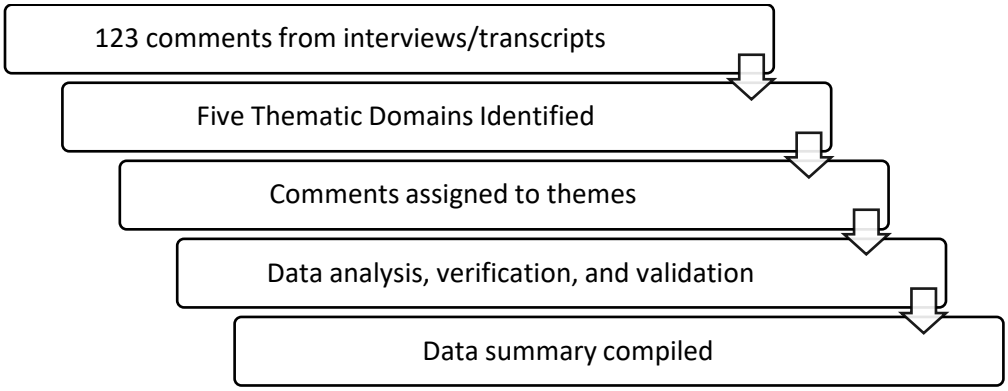
Table 12. Comments per Respondent

Respondent	Comments (n, %)
Stool Bank (Production/Distribution)	30 (24%)
Healthcare Provider	17 (14%)
Healthcare Provider/Researcher	21 (17%)
Patient Advocate	55 (45%)
Total	123 (100%)

Thematic Analysis

Figure 7 shows the overview of the data consolidation and coding process from the unique comments to the themes and summary steps. An overview of the process described from the interviews and background literature has been summarized in a process flow diagram and is described in Figure 8 and addressed in the Discussion section.

Figure 7. Schematic Overview of the Qualitative Data Consolidation Process



Four participants provided 123 unique comments, which were assigned to one or more comment codes; 51 unique comment codes and five thematic domains were identified. The five thematic domains aligned with the high-level steps and domains in the FMT and CDI process, (shown in Figure 8) which are in turn reflected in the process diagram described in this research. The five thematic domains are: Clinical Suspicion and Diagnosis, Decision to Treat, Procurement, Treatment, and Surveillance. A Miscellaneous/General Domain was also included for those comments that did not fit into one or more of the five themes; Miscellaneous/General comments still received a more granular comment code. For the five thematic domains (and the Miscellaneous/General domain), the breakdown of the 123 comments assigned to 290 comment codes is shown in

Table 13.

Table 13. Thematic Domain Comment Totals

Thematic Domain	Total Comments per Domain (n, %)
Clinical Suspicion and Diagnosis	22 (8%)
Decision to Treat	136 (47%)
Procurement	26 (9%)
Treatment	57 (20%)
Surveillance	42 (14%)
Miscellaneous/General	7 (2%)

The 51 unique codes included stakeholders, components, steps, and processes reflected within the larger five domains, as well as any unique codes generated from the interviewee's comments. The top 20 codes and their frequency representing 224 (77%) of the comments are illustrated in Table 14.

Table 14. Top 20 Comment Code Frequency

Unique Comment Code	Frequency (n, %)
Access	43 (15%)
Indication	20 (7%)
Barrier	20 (7%)
Research	14 (5%)
Donor	14 (5%)
Efficacy	12 (4%)
Clinical guidelines	12 (4%)
Treatment	12 (4%)
Stool bank	11 (4%)
Risk	8 (3%)
Oversight	8 (3%)
Safety	7 (2%)
Hospital	7 (2%)
Side effects	7 (2%)
Cure	5 (2%)
Drug Product or Treatment Selection	5 (2%)
Severity	5 (2%)
Cost	5 (2%)
Antibiotics	5 (2%)
Modality	4 (1%)

After each comment had been coded both to a code and a thematic domain, a crosswalk of the results provides a coherent summary of the issues identified by respondents at each step of the CDI/rCDI and FMT process. The results are presented in Table 15 and include a representative or particularly impactful quote from the respondents.

Table 15. Results Crosswalk of Thematic Domains, Comment Codes, and Interview Quotes

Thematic Domain	**Applicable Comment Codes (listed alphabetically)**	**Interview Quote**
Clinical Suspicion and Diagnosis	Contributing factors, diagnostic criteria, exposure and transmission, hospital, incidence, recurrent, severity, symptom onset	*"It is mind-blowing how long an ICU stay [that] a c.diff infection can cause."* *"I take care of a lot of patients with c.diff and see the expenses firsthand: prolonged hospitalizations, prolonged ICU stays, colitis, colectomies, wound care, hospital supplies needed to maintain isolation precautions and to care for and/or control diarrhea-- the list could go on."*
Decision to Treat	Acceptance, access, advocacy, awareness, barrier, clinical guidelines, collaboration, cost, drug product or treatment selection, indication, informed consent, internet, research, standards	*"I just got off the phone. The call I had before you is a woman in North Carolina whose 15-year-old daughter developed C-DIFF after a round of antibiotics for an upper respiratory infection in January and she's on her fourth relapse now. And she's been referred to Duke on Monday for evaluation, for a fecal transplant. And although she's nervous and she realizes that there are inherent risks, she's watching her 15-year-old daughter slip away before her eyes. And that was her take exactly. "I don't care what the risks are at this point. I just want her better.""*
Procurement	Dissemination, donor, stool bank	*"If you do restrict access with stool banks, it's just going to drive people further underground doing it on themselves, which is going to mean an increased use of untested stool, which actually decreases safety. So, you know, I have... I have an issue with that, but I have*

		an issue with people saying that, "This is not a big space". You know, this a big space there's room for everybody at the table." *"At lunch the first day I talked to this doctor, it's like "what is an IND?" I had no idea. And they told me, "well, I have one and it took me 18 months. It took me 600 man hours and it weighs 60 pounds of paper." So I was like that's, doctors can't... Most doctors can't do that. Most doctors are like, "What's an IND?""*
Treatment	Antibiotics, burden, cure, efficacy, externalities, harm, modality, procedure, side effects, treatment	*"It was like a miracle to me. It is amazing. And I hear that over and over and over again from people."* *"This works as close to a miracle as it can be."* *"I ever got c.diff, I would want to receive an FMT from my healthiest family member."*
Surveillance	Adverse event reporting, data, expansion, future considerations, monitoring, oversight, risk, safety, standardization, tracking	*"The alternative is not, "Oh, we'll just wait [for new drugs, scientific advances, policy decisions]." Whilst we're waiting the alternative is death."* *"[Transmission of] an unknown pathogen--that's the worst case scenario [for FMT]."*
Miscellaneous/General	Academia, provider, probiotics, policy	*"I first heard about the therapy from a fellow who had completed residency at another hospital."* *"I became interested as result of […] having a fellow who was interested in IBD."*

Additional Sources Identified from Interviews

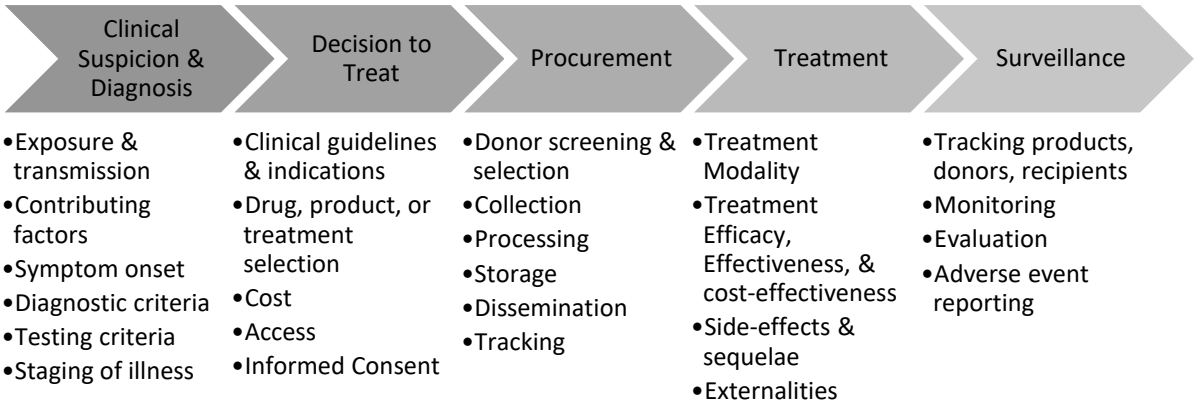
During the qualitative interviews, additional source documents were identified for review. Among those were the transcript from the patient advocate testimony from the first FDA public meeting

and all additional FDA meeting transcripts on the topic of FMT. In addition, the proposed guidance from the FDA on enforcement policy, as well as the proposal for using known donors in FMTs were also reviewed.(*Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies*, 2013; "FDA Regulation of Fecal Microbiota for Transplantation," 2016; "Notice of Proposed Rule Making: Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile. ," 2019) As available, several responses to these FDA proposals from stakeholders that made their letters public and provided oral presentations at the follow-up FDA Listening Session were also reviewed. Last, output from the Microbiome Working Group was reviewed.(D. E. Hoffmann, Palumbo, Ravel, Rowthorn, & von Rosenvinge, 2017) These documents were reviewed, but not coded to the thematic analysis discussed above. The additional qualitative input was used for verification and validation of the thematic domains and unique comment codes, to inform Aims 1 and 2 of the research, and then lastly, to formulate the process map discussed in Chapter 4, Section II.

II. CDI and FMT Process Diagram

A process diagram of the many steps and component elements from potential exposure to *c. diff* to diagnosis, treatment, and surveillance was developed; this diagram serves as a framework to identify and discuss stakeholders and policies and economic factors that impact the spread and treatment of *c. diff*, as well as the use of FMT. The process diagram represents current understanding from the literature and environmental scan, key informant interviews, and modeling and simulation results, and serves as an anchor to summarize and discuss the results of this research. Figure 8 shows a process diagram of the steps and factors in the sequence from exposure and symptom onset for CDI through treatment and post-treatment surveillance.

Figure 8. CDI and FMT Process Diagram



Clinical Suspicion and Diagnosis

The first phase in the process is centered around clinical suspicion of CDI and diagnosis, without which there would not be a need for the process as follows. Factors such as exposure to CDI and its transmission, as well as contributing factors such as recent antibiotic or proton pump inhibitor use, may make a patient susceptible to CDI. Symptom onset includes both the initial GI symptoms and the setting in which symptoms first occur. The settings may be one or more of the following: healthcare facility

onset (HO), community onset healthcare facility associated (CO-HCFA), and community associated (CA) CDI.(L Clifford McDonald et al., 2018) For example, a patient who began to experience severe diarrhea characteristic of CDI at home after an inpatient admission would be considered to have community onset, healthcare facility associated CDI. After symptoms appear, if the patient meets the diagnostic criteria for CDI, the provider should order diagnostic tests which at the present time include a stool toxin test or stool toxin test arbitrated by nucleic acid amplification test (NAAT).(L Clifford McDonald et al., 2018) Upon confirmation of infection, CDI is staged into one of four categories of illness: initial episode non-severe, initial infection severe, initial episode fulminant, or recurrent episodes.(L Clifford McDonald et al., 2018) The stakeholders at this stage are generally limited to the patient, the provider(s) attending to the patient's care, and the lab receiving the specimens and resulting diagnostic test(s).

Decision to Treat

The second phase is the decision to treat. The decision to treat phase of the process includes what the current clinical guidelines and indications are, available drug, product or treatments for selection by the patient and provider, cost of treatment, access to treatment which includes the ability to pay, awareness and acceptability of treatment and access to providers, and finally the informed consent of the patient to accept and undergo the treatment of choice. Stakeholders at this stage are the patient, provider, and their respective networks in which they learn about the availability, acceptability, and access to treatments. These networks may include patients' health insurance and educational resources or patient support groups by medical condition or other affinity grouping—often online—and for providers may include professional networks, boards, committees, and societies.

Procurement

Next is procurement of the treatment, which describes the collection, processing, storage, handling, and dissemination. The stakeholders include pharmaceutical and medical supply companies, collection facilities like blood banks for the collection of blood, and other stakeholders in the supply chain, such as transportation, related to the treatment of CDI. The patient and provider are typically not actively involved in this stage, but can be impacted by shortages, delays, interruptions, or other barriers in the supply chain. However, in the direct, known donor model for stool procurement for FMT, the supply chain is limited to the patient, a known donor, the lab where the donor is screened for diseases that could rule out their status as a donor, and the treatment provider.

Supply chain management for medical and pharmaceutical supplies, devices, facilities, and transportation is regulated and overseen in the U.S. by the FDA. All new drugs and biomedical technologies in the U.S. must pass through the FDA's development and regulatory pipeline.

Treatment

Next is the treatment phase. Factors in this phase are the choice of treatment and modality; treatment efficacy, effectiveness, and cost effectiveness; the side effects and sequalae of treatment choice; and the associated externalities. The patient and provider are critical stakeholders in this phase, but the only factor that is directly within their locus of control is the choice of treatment. All other factors may have significant impact on the patient and provider but are generally outside the immediate treatment window and processes. For example, the average cost to develop and bring a new drug to market is estimated at one billion dollars.(Wouters, McKee, & Luyten, 2020) In the U.S., there are drug patent and exclusivity of production that range from several months to 20 years, depending on drug class, which means that the patent holder retains exclusive rights to manufacture and sell the drug or device during that time to recoup research and development costs.("Frequently Asked Questions on

Patents and Exclusivity," 2020) This monopoly results in a higher price for the treatment. The higher cost of the treatment is generally passed on to the patient in the form of higher copay or coinsurance by the drug manufacturer and the patient's insurance company. While these factors impact patients directly, they are usually in the purview of stakeholders such as researchers, health economists, insurers, policy makers, and scientific review boards and committees.

Surveillance

The last phase in the process is surveillance. Surveillance includes everything post-treatment including monitoring and evaluation of long-term effects and reoccurrence of symptoms, adverse event reporting systems and tracking, and tracking of the treatment products, donors, and recipients. In the US, most post-market surveillance and adverse event reporting is within the purview of the FDA and the CDC. Recently for FMT, the NIH funded a study for the creation of an FMT registry to surveil the delivery of FMTs and to study the long-term effects of FMT. Examples of post-market and population surveillance programs include vaccine side effects reporting via the CDC and FDA device surveillance. General criticism is that surveillance and response is insufficient in the U.S.; criticisms include too high a bar to recall a drug or device, incomplete distribution of newly discovered interactions, warnings, or errors, lax review processes, and lack of timely information about long term effects.(Carpenter, 2006; Health & Services, 2001; Rice, 2015; Bob Roehr, 2012; B. Roehr, 2012) These general criticisms are also germane to the approval and surveillance related to the use of FMT.

III. Health Economic Model

Model Results

Status Quo Scenario

In the status quo scenario, the optimal treatment pathway, or least costly option, was determined to be vancomycin for severe and fulminant CDI and metronidazole for non-severe CDI, respectively. Fulminant CDI was assessed at the second episode of CDI/1st rCDI, as the initial treatment option is singularly vancomycin at a higher dose (500 mg versus 125mg) and metronidazole delivered via IV in the status quo scenario. The results for the status quo scenario show that current clinical practice and treatment results are largely driven by the efficacy of fidaxomicin and vancomycin and the cost of vancomycin. This reflects these antibiotics use as a first line therapy for CDI and rCDI, as recommended in the clinical guidelines and treatment pathways used to construct the model.

Table 16. Cost Effectiveness Results for Status Quo Scenario

Treatment	**Cost**	**QALY**	**ICER**
Non-severe CDI			
Metronidazole	$159	0.7709	Reference
Vancomycin	$674	0.7287	-12,209 (Dominated)
Fidaxomicin	$3,964	0.7945	161,109
Severe CDI			
Vancomycin	$674	0.6477	Reference
Fidaxomicin	$3,964	0.7062	56,186
Fulminant CDI			
Vancomycin (pulse taper)	$1,458	0.5129	Reference
Fidaxomicin	$4,334	0.5999	33,072

The cost effectiveness results for the status quo scenario show that for non-severe CDI/rCDI fidaxomicin is the most costly option, but also the most effective; however fidaxomicin results in an ICER of $161,109 per QALY, which exceeds the threshold of $100,000/QALY, making fidaxomicin an expensive treatment option for non-severe CDI/rCDI. For non-severe CDI, vancomycin is dominated, which means that it is more expensive and less effective, as compared to another option. Vancomycin is dominated by metronidazole for non-severe CDI/rCDI, and metronidazole is the most cost-effective treatment option

for this non-severe CDI/rCDI with a cost effectiveness ratio of $207/QALY (full model output tables are shown in Appendix H. Table 24). For severe CDI/rCDI, fidaxomicin is still the most expensive option, but is more effective than vancomycin and has a far lower ICER than for non-severe CDI/rCDI at $56,186/QALY; vancomycin is the most cost effective treatment option for severe CDI/rCDI with a cost effectiveness of $1041/QALY (see Appendix H. Table 38 for full output). For second line therapy for fulminant CDI/rCDI, fidaxomicin is a cost-effective option at $33,072 (far below the threshold for cost effectiveness), but vancomycin in a pulse tapered regimen is considered the most cost-effective option due to its lower total cost. Vancomycin pulse taper for fulminant CDI/rCDI has a cost effectiveness of $2842/QALY (see Appendix H. Table 51 for full output).

Sensitivity Analysis

One-way sensitivity analysis using 10,000 iterations of microsimulation was conducted; the model was sensitive to the cost and efficacy of vancomycin and fidaxomicin, as well as the probability of death from CDI. Depending on perspective (cost versus effectiveness versus net benefit) the model was also sensitive to the prevalence of non-severe (i.e., mild) and severe CDI (See Figures 9-11). Even varying the efficacy and costs of vancomycin and fidaxomicin, first line antibiotics remained optimal treatment options for CDI and rCDI.

All parameter values for the sensitivity analysis are described previously in Chapter 3, Section II and in Table 19. The full results of the sensitivity analysis, including the results of one-way sensitivity analysis for the variables driving uncertainty in model results, are included in Appendix H.

Figure 9. Status Quo Scenario Tornado Report: Cost

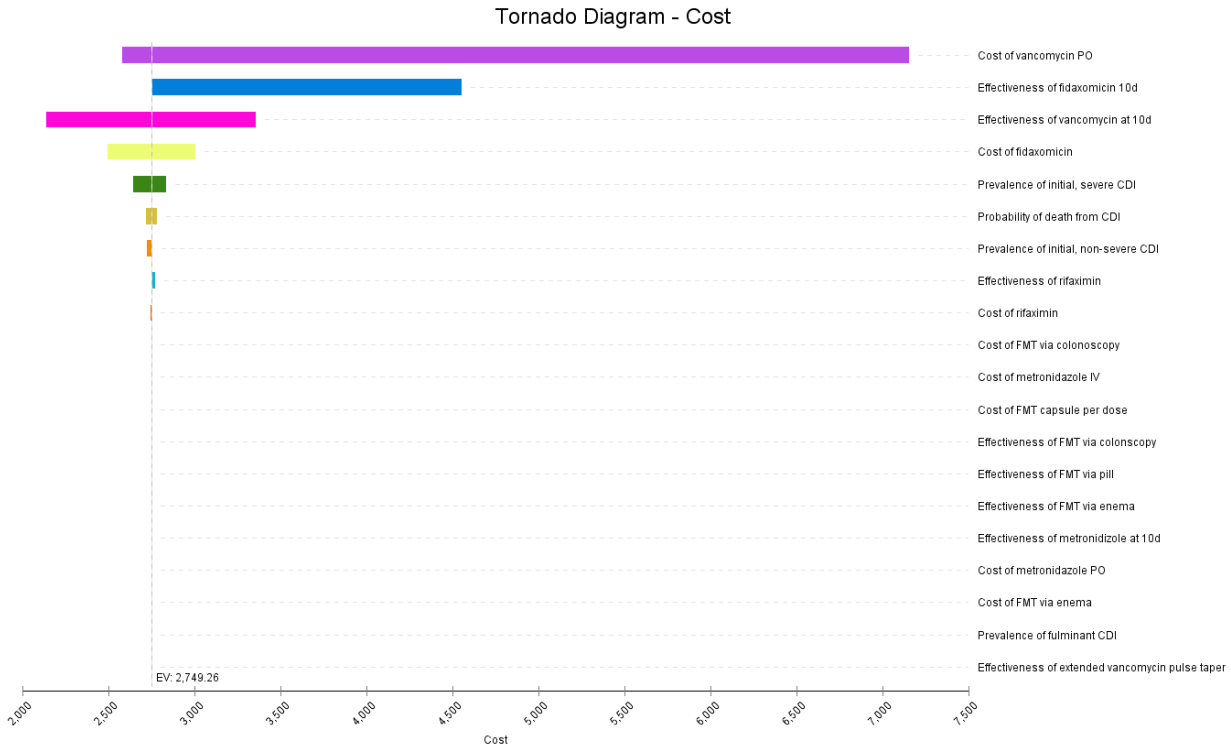


Figure 9 shows the impact on cost for the status quo scenario when varying all model parameters in the sensitivity analysis. For example, in the sensitivity analysis, the cost of vancomycin delivered PO (i.e., via pill) across all stages of CDI/rCDI (e.g., non-severe, severe, and fulminant) varied from $9.70 at the lower limit to $8,228 at the upper limit with the base case set at $313.70, and due to

the large variation, vancomycin was the largest contributor of uncertainty to the outcome of the model (80.5%) (full output shown in Appendix H. Table 66). After the cost of vancomycin, the effectiveness of fidaxomicin and vancomycin contributed uncertainty to the model results—12.6% and 5.7%, respectively. The cost of fidaxomicin is the fourth most influential variable (1%), albeit only nominally. The prevalence of CDI (severe and non-severe) and the prevalence of death from CDI impacted model results nominally (<1%) as compared to the antibiotic therapies. The remaining variables had negligible effect on the model. The full Tornado Diagram output for the status quo scenario regarding cost is shown in Appendix H. Table 66.

Figure 10. Status Quo Scenario Tornado Report: Effectiveness

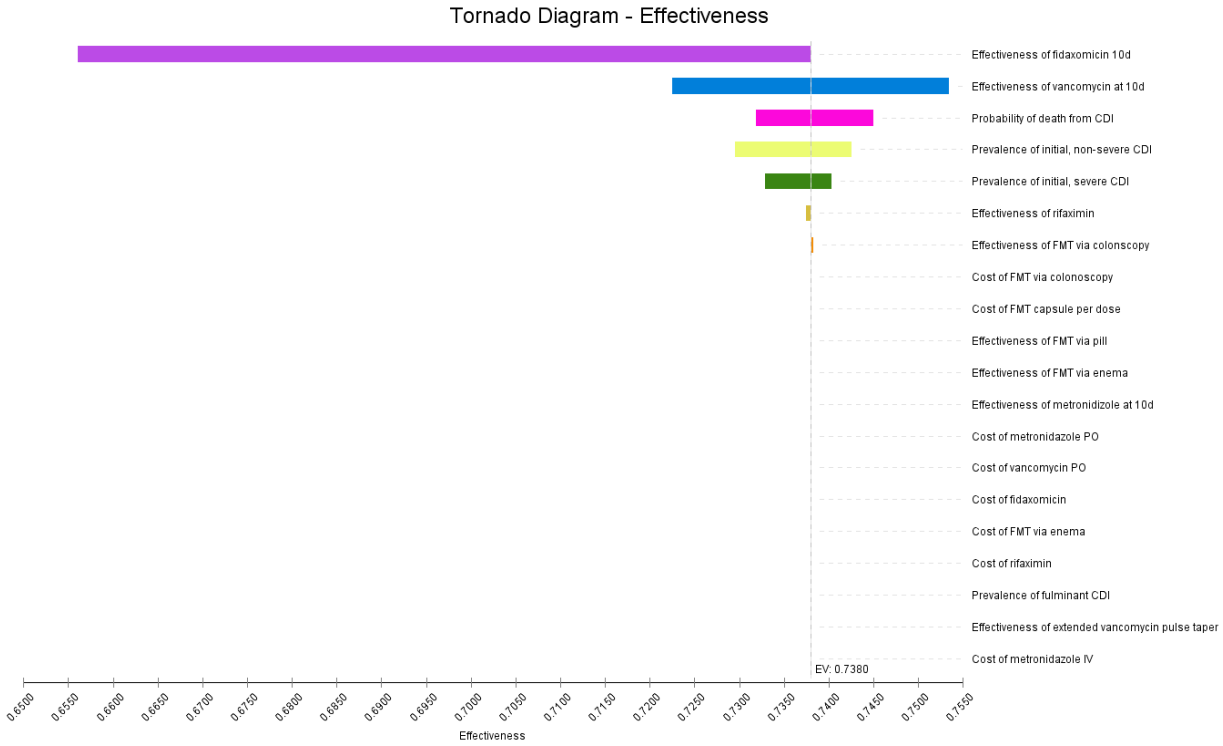


Figure 10 shows the impact on effectiveness for the status quo scenario when varying all model parameters in the sensitivity analysis. The effectiveness of fidaxomicin was the largest contributor of uncertainty to the outcome of the model (83.2%) (full output shown in Appendix H. Table 67). Second,

the effectiveness of vancomycin contributed uncertainty to the model results (11.8%). The prevalence of death from CDI and the prevalence of CDI (non-severe and severe) had a slight impact on model results (2.1%, 2.1%, and 0.7%, respectively). The remaining variables had negligible effect on the model. The full Tornado Diagram output for the status quo scenario regarding effectiveness is shown in Appendix H. Table 67.

Figure 11. Status Quo Scenario Tornado Report: NMB

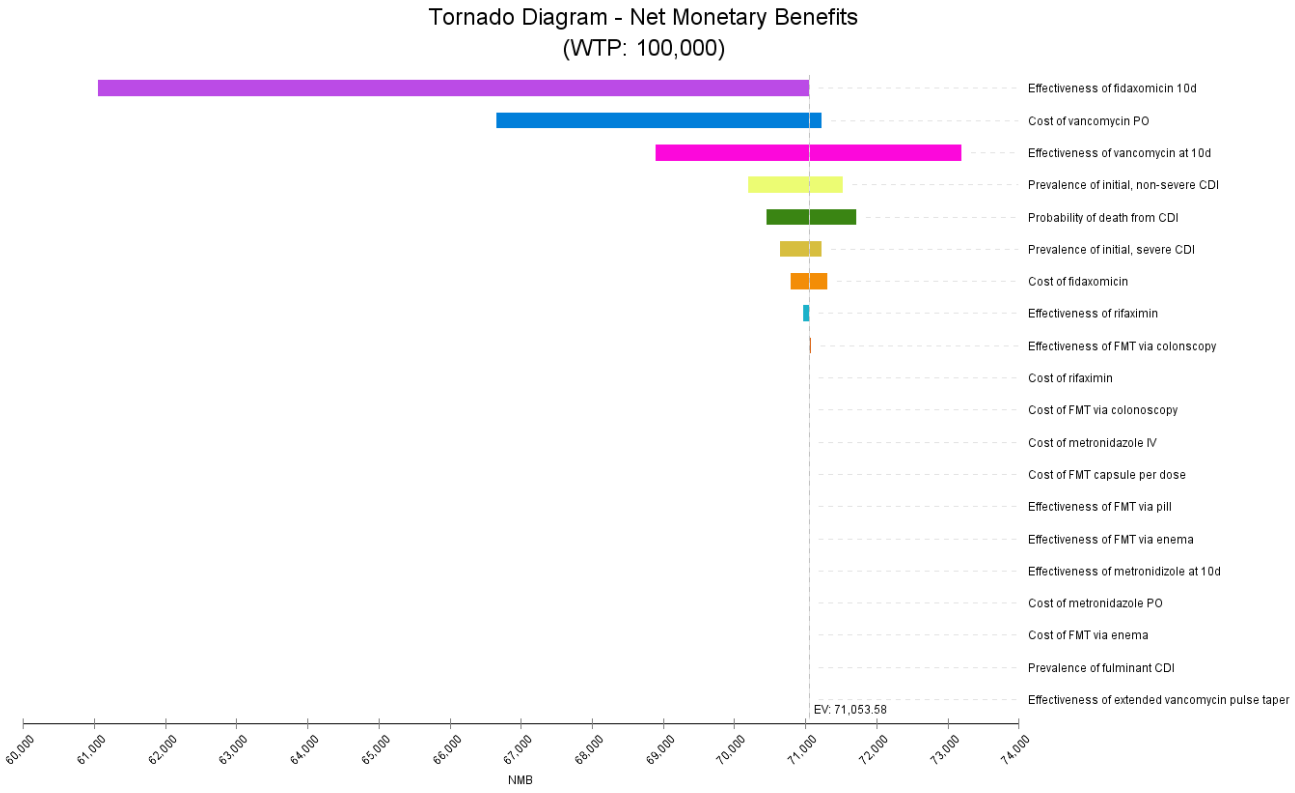


Figure 11 shows the impact on the net monetary benefit (NMB) with the willingness to pay (WTP) set at $100,000 for the status quo scenario when varying all model parameters in the sensitivity analysis. The effectiveness of fidaxomicin was the largest contributor of uncertainty to the outcome of the model (69.7%) (full output shown in Appendix H. Table 65). Next, the cost and effectiveness of vancomycin contributed uncertainty to the model results (14.6% and 13.0%, respectively). The

prevalence of non-severe CDI and prevalence of death from CDI had slight impacts on model results (1.2% and 1.1%, respectively). With regards to NMB, the prevalence of severe CDI had a negligible effect on the model (<1%). The remaining variables had negligible effect on the model. The full Tornado Diagram output for the status quo scenario regarding NMB is shown in Appendix H. Table 65.

Alternative Scenario

In the alternative scenario, the optimal treatment pathway was still determined to be vancomycin for severe and fulminant CDI and metronidazole for non-severe CDI, respectively. In the alternative scenario, fulminant CDI was assessed at the initial episode of CDI to compare the initial treatment options of vancomycin at a higher dose and metronidazole delivered via IV and FMT. Among the FMT options, delivery via enema was determined to be optimal due to its lower cost in comparison to the pill or colonoscopy (not shown).

Table 17. Cost Effectiveness Results for Alternative Scenario using FMT earlier in treatment

Treatment	**Cost**	**QALY**	**ICER**
Non-severe CDI			
Metronidazole	$159	0.7709	Reference
Vancomycin	$624	0.7250	-10,134 (Dominated)
FMT	$2,166	0.7568	-142,661 (Dominated)
Fidaxomicin	$3,964	0.7945	161,109
Severe CDI			
Vancomycin	$674	0.6444	Reference
FMT	$2,166	0.6727	54,468 (Dominated)
Fidaxomicin	$3,964	0.7062	54,051
Fulminant CDI			
Vancomycin & metronidazole via IV	$672	0.5644	Reference
FMT	$2,166	0.5886	61,593

The cost effectiveness results for the alternative scenario show that for non-severe CDI/rCDI fidaxomicin is the most costly option, but also the most effective; however fidaxomicin results in an ICER of $161,109 per QALY, which exceeds the threshold of $100,000/QALY, making fidaxomicin an expensive treatment option for non-severe CDI/rCDI in both scenarios. For non-severe CDI/rCDI, vancomycin and

FMT are dominated, which means that they are more expensive and less effective, as compared to other options. Both vancomycin and FMT are dominated by metronidazole for non-severe CDI/rCDI, and metronidazole is the most cost-effective treatment option for this stage with a cost effectiveness of $207/QALY, as was seen in the status quo scenario (see Appendix H. Table 31). For severe CDI/rCDI, fidaxomicin is still the most expensive option; however, it is more effective than vancomycin, only slightly more effective than FMT and has a far lower ICER at $54,051/QALY as compared to its use for non-severe CDI/rCDI. FMT is dominated by vancomycin in severe CDI/rCDI. Vancomycin is the most cost-effective treatment option for severe CDI/rCDI with a cost effectiveness of $968/QALY (see Appendix H. Table 44Table 51). For a first line therapy fulminant CDI/rCDI, the standard vancomycin plus metronidazole delivered via IV is the most cost-effective option with a cost effectiveness of $1,191/QALY, as compared to FMT which has an overall cost effectiveness of $3,679/QALY (see Appendix H. Table 58). However, FMT meets the cost effectiveness threshold with an ICER of $61,593/QALY (see Appendix H. Table 58) for full output).

Sensitivity Analysis

One-way sensitivity analysis using 10,000 iterations of microsimulation was conducted. In the alternative scenario as in the status quo scenario, the model was sensitive to the cost and efficacy of vancomycin and fidaxomicin, as well as the prevalence of death from CDI (see Figures 12-14). The model was also somewhat sensitive to the prevalence of severe and non-severe CDI. As in the status quo scenario, even with varying cost and effectiveness of currently used antibiotics, antibiotics, rather than FMT, remained the optimal treatment choices for CDI/rCDI.

The full results of the sensitivity analysis, including the results of one-way sensitivity analysis for the variables driving uncertainty in model results, are included in Appendix H.

Figure 12. Alternative Scenario Tornado Report: Cost

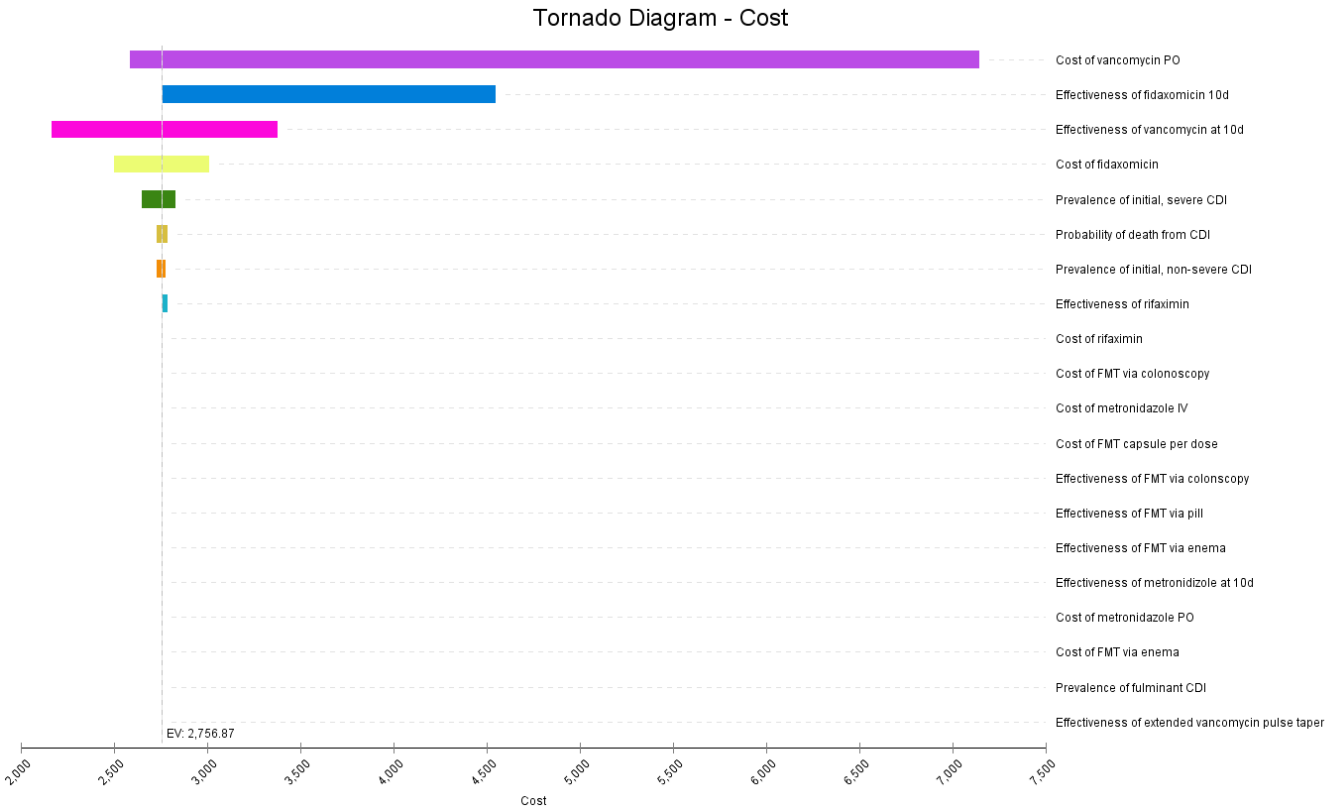


Figure 12 shows the impact on cost for the alternative scenario when varying all model parameters in the sensitivity analysis. The results do not differ significantly from the status quo scenario with the addition of FMT as a treatment option earlier. As in the status quo scenario, the cost of vancomycin was the largest contributor of uncertainty to the outcome of the model (80.6% vs 80.5% in the status quo) (full output shown in Appendix H. Table 69). Next, the effectiveness of fidaxomicin and vancomycin contributed uncertainty to the model results (12.45% and 5.75%, respectively as compared to 12.57% and 5.74% in the status quo scenario). Again, the cost of fidaxomicin is the fourth most influential variable (1%), albeit only nominally. The prevalence of CDI (severe and non-severe) and the prevalence of death from CDI impacted model results nominally (<1%) as compared to the antibiotic therapies. The remaining variables had negligible effect on the model. The full Tornado Diagram output for the status quo scenario regarding cost is shown in Appendix H. Table 69.

Figure 13. Alternative Scenario Tornado Report: Effectiveness

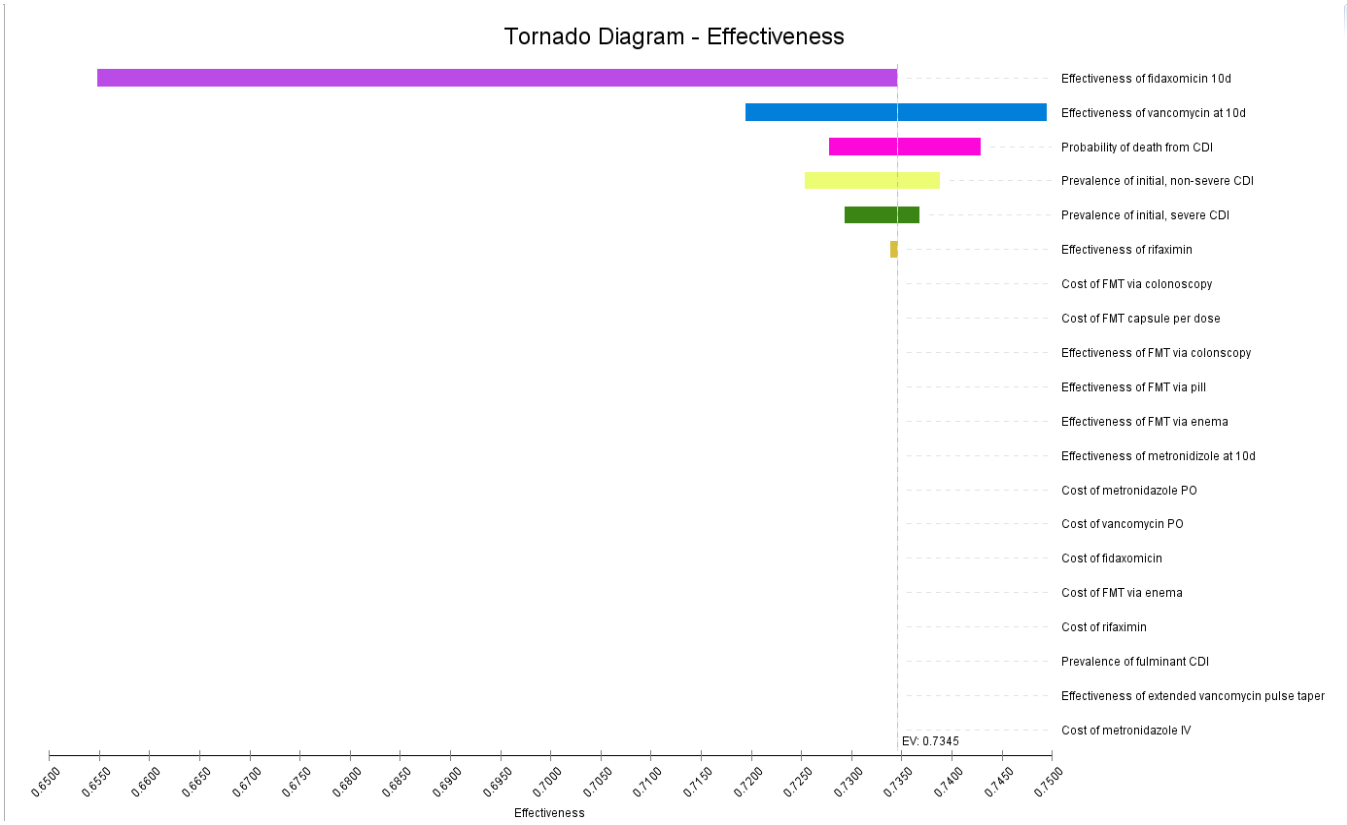


Figure 13 shows the impact on effectiveness for the alternative scenario when varying all model parameters in the sensitivity analysis. The results of the sensitivity analysis regarding the impact on effectiveness did not differ substantially in the alternative scenario as compared to the status quo. As in the status quo scenario, the effectiveness of fidaxomicin was the largest contributor of uncertainty to the outcome of the model (82.3% versus 83.2% in the status quo scenario) (full output shown in Appendix H. Table 70). Second, the effectiveness of vancomycin contributed uncertainty to the model results (11.7% versus 11.8% in the status quo scenario). The prevalence of death from CDI and the prevalence of CDI (non-severe and severe) had a slight impact on model results (3.0%, 2.4%, and 0.7%, respectively versus 2.1%, 2.1%, and 0.7% in the status quo). The remaining variables had negligible effect on the model. The full Tornado Diagram output for the status quo scenario regarding effectiveness is shown in Appendix H. Table 70.

Figure 14. Alternative Scenario Tornado Report: NMB

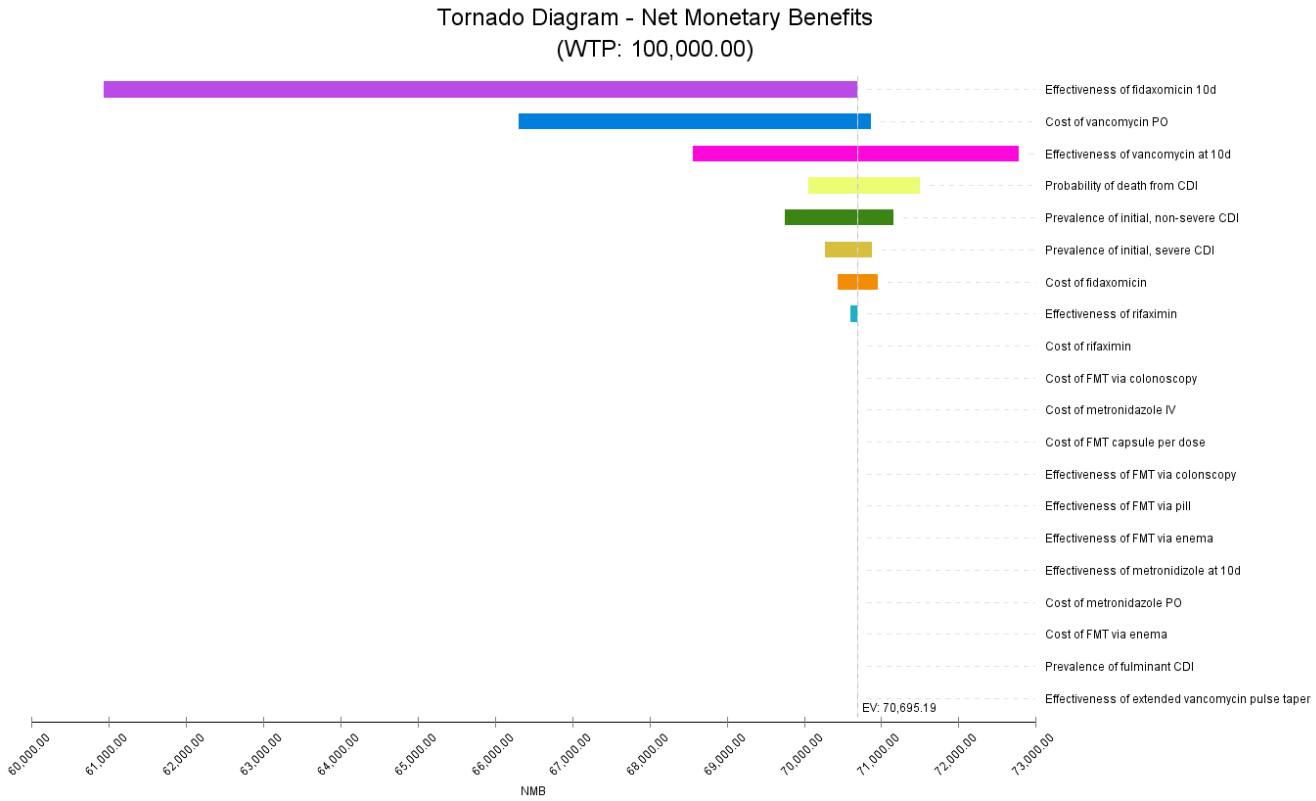


Figure 14 shows the impact on the net monetary benefit (NMB) with the willingness to pay (WTP) set at $100,000 for the alternative when varying all model parameters in the sensitivity analysis. As in the status quo scenario, the effectiveness of fidaxomicin was the largest contributor of uncertainty to the outcome of the model (68.8% versus 69.7% in the status quo) (full output shown in Appendix H. Table 68). Next, the cost and effectiveness of vancomycin contributed uncertainty to the model results (15.0% and 12.8%, respectively). The prevalence of death from CDI and the prevalence of non-severe CDI had slight impacts on model results (1.5% and 1.4%, respectively as compared to 1.2% and 1.1% in the status quo). With regards to NMB, the prevalence of severe CDI had a negligible effect on the model (<1%). The remaining variables had negligible effect on the model. The full Tornado Diagram output for the status quo scenario regarding NMB is shown in Appendix H. Table 68.

CHAPTER 5. DISCUSSION OF RESULTS AND POLICY IMPLICATIONS

Summary of Study Results

The goal of this research was to explore the policy and economic implications of expanded use of fecal microbiota transplantation, using CDI as a use case.

Aim 1: Review the current state of the literature and findings about CDI and fecal transplants, especially focused on a review of the policies and regulations that pertain to the classification and use of feces.

The literature shows that CDI and rCDI are highly infectious healthcare associated infections that cause a high burden of costs to the healthcare system and significantly increase morbidity and mortality. Clinical research on the microbiome is rapidly advancing our understanding of its role in the immune system and disease. The burgeoning field offers great promise and is only beginning to tackle the potential applications and uses of microbiota transplantation. Stool for use primarily in FMT is currently categorized and regulated most often as a drug. However, other regulatory frameworks may be more fitting to accommodate regulating the process of stool production, appropriate oversight of and access to treatment, and the abundance of unscreened, untreated, unprocessed stool available to patients outside the medical system. Research published by Scheeler in November of 2019 provides a robust summary of the current global regulatory issues and landscape.

Aim 2: Identify key issues and barriers in gut biome research, potential applications in healthcare innovation, and fecal transplants as a treatment option.

With regards to key issues and barriers in gut biome research, the research field is learning and adapting at a frenetic pace that has accelerated in the past ten to 15 years. New developments and applications of treatment and technologies will continue to grow, and microbiome-based therapies targeting the gut and other body systems offer new tools to combat puzzling infections.

Regarding healthcare applications of innovations, the current and future policy and regulatory environment requires speed, flexibility, and the ability to provide oversight against novel threats as well as access to life-saving treatment. With respect to the health economics of new innovations, externalities such as the threat of antibiotic resistance and the emergence of new novel pathogens need to be accounted for in assessing the utility of new treatment options and innovative applications.

Regarding fecal transplants as a treatment option, currently clinical trials support the safe and effective use of FMT for rCDI, as well as other acute indications like UC. However, the use of FMT is not widespread and is still being researched. The primary threat to the uptake of FMT and diffusion of the innovation is the perceived risk of unknown pathogens, such as antibiotic resistant *E. coli* and COVID-19.

Aim 3: Develop an economic analysis of the expanded use of FMT to treat CDI in the United States, as compared to current standard treatment options.

In summary, the current treatment model is driven by the relatively high effectiveness and low cost of antibiotics, namely fidaxomicin and vancomycin. However, as the effectiveness of antibiotics decreases or costs increase, better less expensive treatment alternatives to current antibiotics will be needed, but are not yet available.

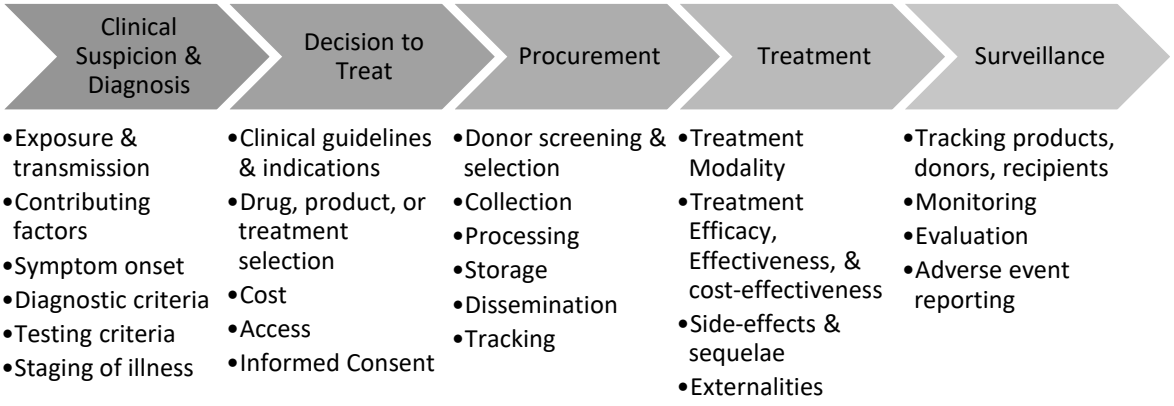
Implications for Policy Development and Implementation

With regards to implications for policy development and implementation, we can discuss these for each of the components identified in this research: the overall process, the problem, the stakeholders, FMT specifically as a treatment option in the solutions stream, the economic model, and the overarching policy window that shapes the future of FMT use.

Discussion of the Process Diagram

The process diagram was developed to summarize the steps and components within each step of the process from CDI exposure to treatment and post-infection or treatment surveillance. However, the same process steps and components could be applicable and customizable to any disease or infectious pathogen. The process diagram offers a concise, cohesive, holistic summary of the myriad, often concurrent and parallel dynamic processes that should be considered when approaching research, clinical care, and health policy interventions.

Figure 15. CDI and FMT Process Diagram Revisited



In healthcare and medicine, the oft-cited time from scientific finding to adoption in clinical practice is 17 years, although the range of time to adoption varies widely. Time and rate of adoption are widely distributed ranging from several months to hundreds of years and vary by domain, as well as outcome. Negative or null results have a lower average time to diffusion (i.e., six to eight years), but there are many complexities that factor into rate of adoption. The cumulative progression for an individual or population through each step in the process described above could result in a variety of outcomes depending on factors such as the speed of adoption of innovations like FMT. Significant policy and research efforts have been made to speed the time to adoption of life-saving drugs and therapeutics, such as provisions in the 21st Century Cures Act that specifically address accelerated approval, streamlined data review, and faster patient access to treatments, including for

"compassionate use" which is what FMT for CDI has been granted. Research efforts such as investments in translational and implementation science also aim to help speed and scale the adoption of proven evidence-based interventions.

With regard to the Rogers Innovation Development Process, CDI seems to be in the 6th stage—consequences—in the U.S.; the spread and rate of CDI has plateaued, there are known preventive measures to take in hospital settings, and treatment is available. However, with the rise and spread of multidrug resistant organisms (MDRO), healthcare is beginning to reckon with the consequences of using multiple rounds of antibiotics for treatments, especially when those antibiotics may contribute further to the rise and spread of MDRO immune to available therapeutics. As for the gut biome and FMT, it is in stages 2 and three—basic and applied research and development. While FMT solution and capsules are in production via stool banks, FMT has not yet reached the stages of full commercialization, as it is still being tested in clinical trials and has restricted application only for rCDI.

FMT research is still in its early stages and lacks comprehensive large-scale long-term studies and follow up. Given that the mechanism of action is not yet well understood, nor do we understand how colonies and profiles of bacteria interact and/or change between the donor(s) and recipient, there is still great uncertainty about the consequences of FMT at the individual level. An ethics paper discusses numerous ways in which the ethics of the use of FMT are challenging because the trade-offs and various consequences are not yet entirely understood.(Y. Ma et al., 2017) In addition, most who currently use FMT are severely ill and running out of therapeutic options—thus making the decision to use FMT without being able to fully understand the consequences more challenging.

At a macro scale, the policies governing procurement, production, distribution, and use of stool and FMT have consequences of all three types mentioned above. Expanding the use of FMT, even if only for CDI, reduces the amount of antibiotics needed to treat the infection, thus reducing risks of

developing or spreading MDRO which would be highly desirable. Alternatively, if FMT is restricted either due to increased enforcement action on stool banks or increased cost of treatment, patients may opt to go the riskier DIY route out of desperation—an undesirable consequence of restrictive FMT policies. As knowledge of infectious diseases and their interactions in the GI system are better known, FMT donors and donations undergo greater scrutiny, testing, and quality control and surveillance; as the manufacturing process becomes more technological for the sake of safety (a desirable outcome), it also becomes more costly to produce, an indirect consequence. Again, as knowledge and discovery of infectious diseases expands, such as in the case of the COVID-19 pandemic or the 2019 transmission of drug resistant E. coli bacteria via FMT, there has been a direct consequence of having to quarantine or recall products for additional testing.(DeFilipp et al., 2019; Gu et al., 2020; Xiao et al., 2020)

With any new innovation, especially one like FMT where the mechanism(s) of action are not yet fully understood, there is the opportunity for surprising unanticipated consequences; in this field of research, unanticipated consequences of FMT have been reported as medical case reports. For instance, there is a case report of a patient with alopecia who began to regrow hair after an unrelated FMT procedure.(Rebello, Wang, Yen, Lio, & Kelly, 2017) However there have also been reports of formerly thin patients gaining weight rapidly after receiving an FMT from an overweight donor and evidence from animal models that anxiety symptoms may be passed via FMT from donor to recipient.(Alang & Kelly, 2015; N. Li et al., 2019; Zhao et al., 2020) As the anecdotes accumulate, it has the anticipated consequence of allowing researchers to piece together scientific theories and evidence to further our understanding of the role the gut biome plays in our health and well-being. Medical professionals and researchers are cautious about FMT due to the lack of quality and safety data and understanding of the short- and long-term consequences. Conversely, public awareness about FMT has grown over the last five to ten years due to national public interest and discussion in the media.

With regards to policy development and implementation, policy changes could be targeted at any step or component in the process, individually or multiple at a time, and impact the process of contracting, identifying, and treating CDI, or any condition, with FMT. For example, adopting a requirement of using a known donor model would significantly alter the time and patient burden to identify a donor, screen the donor stool, and does not make provisions for long-term monitoring and evaluation of effects. The adoption of a nationally coordinated stool bank, similar to the Red Cross for blood donations, would require sophisticated coordinated procurement, processing, tracking, inventory, and quality control management. Public health interventions such as mandated hospital reporting of HAI and tying value-based payment to quality scores determined based on HAIs, among other metrics, has had the added benefit of causing an increase in awareness while simultaneously reducing infection rates. More real time, granular, actionable, publicly reported public health and healthcare data may drive further improvements in quality measures. Similar transparency efforts through data reporting strategies could also be undertaken for other components within the process diagram, like how research studies are now catalogued and displayed publicly on clinicaltrials.gov or how CMS now publishes drug cost and utilization data publicly. When there is a clear, coordinated, consistent approach—namely at the federal level, but also relevant to the state and local jurisdictions—for the policy strategy across the lifecycle and breadth of processes that impact disease is when significant advances to combat illnesses are made.

Discussion of the Problem

Within the context of *c. diff* and FMT, there are many problems in play. *C. diff* has significant morbidity and mortality and rCDI lacks effective treatment, which are problems for both patients and providers. When traditional treatment is effective, traditional treatment relies on increasing use of high dosages of antibiotics, which puts both the patient and the healthcare system at risk of contributing to

the rise of antibiotic resistant diseases. Awareness of *c. diff* as an HAI has risen in prominence both because of mandated infection reporting (i.e., a policy) and an international increase in the prevalence of the disease due to emerging virulent strains; growing awareness has brought the problems of CDI, increasing virulence, HAIs, and the burden of mandated reporting to the forefront of the problem discussion.

With regards to problems facing FMT, there are several. Within the healthcare system, procuring a sample for FMT and the supply chain management necessary for ease of uptake and administration was a problem that OpenBiome, the largest stool bank currently in operation sought to solve. However OpenBiome has faced criticism from industry stakeholders that they are not compliant with FDA guidelines and faces competition from makers of synthetic stool and probiotic-enhanced stool. As such, if this one venture were to cease operations, the U.S. would not have a secondary reliable distributor of stool at scale. With stool, there are the issues from a scientific and manufacturing perspectives that stool is composed of heterogenous and biodynamic material that is not yet well understood and cannot be reliably replicated; as such, production still relies on individual contributions, and the risk of unintended consequences of using a poorly understood treatment is unknown. In addition, FMT faces the problem of a "yuck factor" that is unique to this treatment. Using the problem stream framework from Kingdon, many of the problems surrounding CDI and FMT are described in Table 18 to provide context for this research.

Table 18. CDI and FMT Problem List

Focus	**Problem List**
Individual	• CDI causes significant morbidity and mortality including poor QoL • CDI typically occurs after antibiotic use (so after a preceding infection/illness) • Access to care and treatment in the U.S. is variable, dependent on providers and insurance • CDI adds days and cost to admissions and total healthcare expenses, which is burdensome to patients and families

C. diff	• Gram+ bacteria which makes it impervious to alcohol handwashing and requires traditional soap and water handwashing and special treatment of surfaces to remove spores from surfaces • Highly contagious and increasingly virulent
Treatment for *c. diff*	• Treatment requires more and higher doses of antibiotics • Antibiotic therapy contribute to antibiotic resistance including multi-drug resistant organisms (MDRO) • Recurrence of CDI is 20%, which is high, making multiple treatment rounds common
Healthcare system	• *C. diff* is a prevalent HAI • Treatment availability and acceptability are largely determined by health insurance payments • CDI adds potentially preventable days and cost to admissions and total healthcare expenses
FMT	• Dynamic nature of bacteria in stool is not yet fully understood and is hard to replicate • Regulatory status is currently undecided and subject to change • If safe FMT is inaccessible within the healthcare system, available alternatives include at-home DIY treatment using a friend or family member's stool • FMT may be risky regarding spread of pathogens if done as an at-home DIY treatment • Stool has a "yuck factor" that can currently be overcome for a severe and debilitating or potentially fatal illness • Side effects and long-term effects of FMT are currently unknown

Clearly, with the rise of MDRO, the emergence of novel pathogens, and the poor quality of life of those with chronic conditions that are mediated in the gut, such as Crohn's or obesity, new and innovative treatment options are necessary. Viable treatment options that percolate at the fringes of society and are diffused by innovators and early adopters via niche forums like disease specific online communities can be tested and evaluated and diffuse into mainstream science and clinical practice, as FMT has done.

Additionally, provisions in the 21st Century Cures Act provide for fast-track research and evaluation options for urgently needed treatment options that are developed in response to novel pathogens and emerging epidemics, as CDI was in the early 2000s. As antibiotic resistance spreads, but we simultaneously better understand the role of probiotics and commensal bacteria, scientists, clinicians, and policymakers will need new approaches to treat individuals, animals, plants, and even

environments (e.g., soil) with bacteria inoculations to combat disease and promote health. As the economic model in this research has demonstrated, the status quo scenario is currently driven by the cost and efficacy of antibiotics; however, the scales change dramatically when the costs to treat rise and the efficacy dwindles. However, this research indicates that this has not happened yet and is unlikely to until the costs of FMT fall dramatically or the costs and efficacy of antibiotics become prohibitive against CDI. When time constraints and acuity increase the urgency for treatment, such as when the duration of illness shortens or patient deterioration has rapid onset, other effective treatment options are needed.

With regards to policy development and implementation, the passing of 21st Century Cures Act is only one step toward addressing the policy levers needed to address the problems of emerging novel pathogens that cause epidemics and pandemics, the need for more effective treatment options that do not increase the risk of antibiotic resistance, and treatment options to improve quality of life for those with difficult to treat acute and chronic conditions. Policy makers need to balance safety and effectiveness of speeding new pharmacological and therapeutic options to market while including provisions for short- and long-term study of effects, particularly on populations and communities that are not historically well represented in scientific research. If given the opportunity, policy makers at the local levels, such as hospitals and providers, can adopt practices that promote good stewardship of the resources we currently have that may help delay the worsening of problems—for example, the adoption of antibiotic stewardship programs in hospitals as well as community and industrial settings, like agriculture.

Discussion of the Stakeholders

With respect to this research, the active participants are: individuals/patients and families; providers in the healthcare system, including academic medical centers and clinical researchers; suppliers of treatment and medical equipment including pharmaceutical companies and stool banks;

legislative and regulatory agencies; specialty societies and clinical guideline committees; patient advocacy and affinity groups with an emphasis on groups that have convened via social media specifically around FMT; health insurance payers; and monitoring/surveillance and research funding agencies.

Kingdon refers to certain groupings of these stakeholders as "policy communities." In the context of this research, the policy communities are fragmented, or more commonly referred to as "siloed." The policy communities span multiple settings, expertise, and even various industries, each with its own policies and governing agencies. The larger and more diverse the policy community, the harder it is to converge on a policy issue and advance a single cohesive timely policy agenda. The policy communities identified as active participants throughout this research, as identified via the process diagram, are:

- Federal agencies, including the FDA, NIH, CDC, and CMS
- Academic medicine institutions
- Researchers, including disease-specific researcher communities
- Venture capital start-up pharmaceutical companies and industry representatives
- Stool banks
- Providers and healthcare systems
- Specialty societies
- Evidence-based practice guideline committees
- Patient and disease special interest groups and advocates

With regards to the economic model, the actions and consequences for the stakeholders are being influenced by the economics within the current healthcare system. The model presents a simplistic depiction of the current scenario and hypothetical alternative state. Stakeholders may react to

the model based on their unique perspectives, and a more robust model would incorporate feedback from a wide variety of stakeholders, as well as validate the results with a cross-section of stakeholders. Economic modeling and performing multiple iterations of hypothesis testing are promising strategies to convene stakeholders around a problem set, select and test various solutions, generate buy-in across various stakeholder groups, create a solid foundation from which to facilitate opening the policy window and present a well-developed policy solution for implementation; this strategy could be illustrative for the FDA, pharmaceutical and stool bank companies who are developing FMT products, healthcare practitioners, and patient advocacy groups as policy and practice changes are considered.

However, the economic model, as well as current practice, demonstrates that there is significant variance in costs and effectiveness of available treatments. There are economic incentives for developing new technologically advanced expensive treatment options, similar to the approach of chimeric antigen receptor T-cell (CAR-T) therapy for cancer but as applied to CDI and other gut mediated illnesses, while taking advantage of exclusivity and significant financial opportunities. Pharmaceutical and R&D companies are not incentivized to bring therapies such as FMT to scale at an accessible cost; FMT-derived therapies developed for CDI/rCDI may fall under Breakthrough Therapy Designation and/or Orphan Drug Designation as granted by the FDA. When an FMT-derived drug or biologic treatment option received these designations and patent exclusivity for producing the product, the patent holder and manufacturer will have a de facto corner of the market. As such, the stakeholders involved in drug lobbying, development, and manufacturing are powerful and looking to maximize profit through any available policy levers.

Discussion of FMT as a Treatment Option

FMT as a treatment for CDI, rCDI, and other GI afflictions is but one promising option in the "solutions stream." FMT offers a widely available and accessible treatment option, albeit not without

risk. However, recipients may consider some of those risks, as an acceptable trade-off for a better quality of life, significant reduction in morbidity, or avoidance of death, even if faced with the option of riskier FMTs like DIY FMT enemas without screening the donor. As the Diffusion of Innovation Model and the Kingdon's Policy Streams and Window Model show, matching problems to viable solutions that result in policy change is highly dependent on existing communication channels and the messaging of key stakeholders. With the proliferation and increased voice of patient advocacy groups that can speak out directly online, conversations about suffering and treatment are increasingly shaped by the patient voice and experience, which can have positive effects on raising awareness and creating conditions for positive policy change. In determining policy, a single, well-timed, powerful story has as much weight as a control trial or systematic literature review and meta-analysis; both are equal to one observation.

A driver in the diffusion of FMT as a treatment for rCDI has been the internet, specifically websites and online patient communities that serve to discuss treatment for rCDI or promote FMT. Patients and families can access information not previously available to them or their care teams via the internet. Patients and patient advocates report anecdotes of searching for information online in times of great distress or as a last resort when all other treatments failed, and finding online do-it-yourself (DIY) instructions on how to perform FMT at home, resulting in treatment patients believe to be life-saving or curative, but could potentially also be dangerous. While the internet may not be a reliable source of accurate information for CDI/rCDI and FMT treatment, nevertheless, it is accessible and is widely used. More formal means of communication regarding testing FMT is the cataloguing of RCTs and ability to search trials on clinicaltrials.gov. Clinicaltrials.gov "is a database of privately and publicly funded clinical studies conducted around the world" where there are currently "326,612 total research studies in all 50 states and in 209 countries" registered to peruse. Of those, 327 include FMT as an area of study as either the condition or intervention of interest (as of January 2021).

FMT is one of many new treatment options, such as biologics that are dynamic and responsive to the recipient's pathology and biology. With advances such as the use of genomics for personalized medicine or the use of artificial intelligence and machine learning in medical devices or customized profiles of probiotic supplements, technologically advanced and innovative treatment options will continue to be less and less adherent to strict pharmacologic classification and regulatory schemes. In addition, as therapeutics become more advanced technologically as well as more customized to the individual, there is a concern that costs will balloon substantially. Growth in usage of and drug prices for biologics has increased drastically and will continue to rise if left unchecked. With regards to policy development and implementation, affordable, effective treatment options must be available and accessible for the general population, and it is imperative that disadvantaged populations have equitable access to novel lifesaving treatment options.

Discussion of the Economic Model

With regards to the economic analysis, the models show that current and future treatment options are driven by the cost and efficacy of antibiotics, namely vancomycin. As the efficacy of antibiotics decreases, other antibiotics are currently available for CDI and rCDI treatment. We are not yet at the point where FMT becomes a cost-effective alternative treatment option for CDI and rCDI, and more research is needed in the future if circumstances change significantly. Economic modeling should be used prior to the deployment of significant practice changes to ethically and robustly test changes "*in vitro"* rather than in patients; the results of economic models and patient simulation should then inform further testing in patients, and later inform policy development and implementation.

In addition, FMT procurement and distribution has halted due to concerns that COVID-19 can be spread via the GI system. Given the rapid adoption of FMT and rapid growth of OpenBiome since its inception in 2012, it is likely that FMT is approaching the cusp of the tipping point for the diffusion of the

innovation; if momentum is just below the cusp, the shut down due to COVID-19, plus the prior year's transmission of drug resistant *E. coli*, may be a chilling effect on future diffusion and adoption. However, if momentum is beyond the tipping point, and can be paused or sustained beyond the pandemic times, FMT will continue to spread and gain traction in research, clinical, and patient communities. This seems to be a pivotal time in the diffusion of this innovation, and it remains to be seen if adoption of FMT will be brought to scale.

With regards to policy development and implementation, the results of the healthcare economic analysis show that while FMT is an important treatment option for rCDI unresponsive to other therapies, it is currently not feasible nor practicable that FMT would be a cost-effective alternative treatment option to antibiotics for CDI and rCDI. Other emerging technologies and applications will certainly arise in the future, especially with respect to dynamic therapies that alter the microbiome or other bodily processes to achieve improved health and wellbeing, that will require special policy considerations for implementation.

Discussion of the Policy Window

Within the context of FMT, an article in the New York Times in 2019 reported on a shift in the policy, problem, and politics stream. The article reported that the FDA was nearing a final decision in their review of the classification of stool, and provided opinions from stakeholders including patients who have been cured with FMT, healthcare providers, researchers, and pharmaceutical companies who have invested in developing new microbiota therapies.(Jacobs, 2019) The article identified the problems of antibiotic use and the *c. diff* epidemic in healthcare, difficulties with treatment including poor HRQoL and multiple rounds of treatment for patients with CDI, and potentially limiting access to lifesaving treatment due to pharmaceutical exclusivity patents depending on the final classification of stool; the author discussed potential policy solutions that have been proposed by the policy community such as

the FDA creating a new classification and increased scrutiny of the country's only public stool bank, OpenBiome.

With the announcement that the former FDA Director Scott Gottlieb was stepping down within the same week, it appeared that there were several shifts in the streams happening concurrently. However the FDA has yet to release final guidance—a signal that convergence has not yet occurred and the policy window has not yet opened for the FMT regulatory status. With a recent election year and an ongoing global pandemic, it is highly unlikely that any attention will be given to CDI or FMT directly. If any positive policy change occurs, it will be ancillary to the pandemic and as a result of policy changes directed at COVID impact or recovery.

Regarding policy development and implementation, before the U.S. reaches a tipping point, policy makers should act to adopt agile and flexible regulatory frameworks for classifying, evaluating, and regulating new and novel pharmaceutical and therapeutic treatment options. Manufacturers and policy makers also need to consider the financial impact, as well as ensure fast and equitable access to new and novel treatments, especially for conditions with high morbidity and mortality.

With regards to Diffusion of Innovation and the policy window, the innovations of FMT and microbiome therapy have gained traction in the research community and spread significantly in the last decade. Several times in the last few years, the FDA has made movement to finalize regulatory oversight regarding FMT; however, the policy window never materialized fully. With the emergence of COVID-19, the focus within the healthcare system, researchers, and policymakers alike has shifted and adapted significantly to adapt to the pandemic and there hasn't been bandwidth or urgency for other issues.

Strengths and Limitations

Strengths

There are many strengths of this research. The use of FMT is a timely topic, as is the conversation regarding the economic and policy implications of its use. During the time this dissertation research was conducted, new and emerging research was rapidly being developed and published. Experts and policy makers in the field and at the front lines recognized the need for national leadership and well-designed RCT studies to inform decision making.

While CDI was the use case identified for this research, and while FMT is currently a unique treatment in its classification and use, medicine and public health will continue to develop innovative technologies and treatments. These new treatments may not be conventionally understood and classified and will need agile generalizable frameworks and analytic methods to evaluate and test their impact, such as those used in this research.

Research regarding FMT sits at the nexus between advances in biomedical sciences and genomics research, clinical care delivery, policy and regulation, and the patient experience. In addition, the issue of FMT and its use for CDI touches many settings, processes, and local and federal policy-making entities. This critical intersection, the complexity, the high stakes, and rapid timelines in each domain makes it a topic opining for leadership from the public health research and policy community.

Limitations

There are also significant limitations to this research. First, there are threats to the internal validity, specifically the maturation of the topic over time and group composition effects. The field is rapidly advancing and evolving and cannot be considered exhaustive or conclusive. Regarding the group composition and its effect on progression and maturation over time, the field is growing but is still fairly

small. Certain stakeholders in the group have collaborative or adversarial relationships that can influence culture, policy, progression, and maturation of ideas and science within the field. As the topic matures over time, as it did over the course of the thesis research, conclusions will be drawn and redrawn many times and influenced by stakeholder perspectives before being considered definitive. During this dissertation research (and independent from it), several large grants were awarded, and significant papers published that significantly advanced the field of FMT policy and economic research, as well as clinical practice.(D. Hoffmann et al., 2017; Diane E. Hoffmann, 2015; D. E. Hoffmann et al., 2017; A. Scheeler, 2019; Wu et al., 2016) Some of the concepts originally conceived of as novel in this dissertation research became stale as the field progressed.

Separately, in spring of 2020, the SARS-CoV-2 COVID-19 pandemic hit the United States. With the potential spread of disease through fecal matter, stool donation and shipping at the U.S.'s largest stool bank was halted and samples quarantined until stool could reliably be tested for the virus and the manufacturing process adequately updated to accommodate potential increased risk and tracking requirements. Within the study and research of FMT, gut biome functioning and role in the immune system, and infectious diseases, the rise of COVID-19 presents interesting policy, operational, and clinical considerations that are not an immediate threat to the internal validity of this research, but will significantly impact the field in the short- and long-term horizons.

As CDI and rCDI are particularly devastating for patients, sometimes with little hope of recovery, there is also the possibility that those who choose FMT as a treatment of last resort are simply desperate for any relief, hope of improvement, or recovery and this may bias the overall impression of the treatment. It is possible that because the treatment group is composed of very sick individuals with significantly altered and depleted biomes, researchers may see more positive efficacy with FMT as it does a "full reboot" of the recipient's gut biome, whereas the treatment would be less efficacious in the

general, much healthier population with more stable, normal biomes. Within the context of this research, interviewees who stated that FMT was as "close to a miracle" as a therapy likely formed that opinion both from the scientific evidence, but also from personal experience seeing FMT's restorative impact for patients.

Regarding threats of external validity, both non-representative sampling and non-representative context are threats within this research. Those considering or receiving FMT are far sicker and more desperate for effective treatment than the general population. This was demonstrated during the interviews, and may have biased the qualitative data towards positive results from FMT. Stool donors may be a non-representative sample and different from the general population; the criteria for donation are stringent and the acceptance rate among potential donors is low. There is little available data on individual donor characteristics, and even less available data on the donor biome profiles and dynamics or interactions with the recipient's biome. Some have argued for more stringent criteria for donors, including exclusion criteria such as antibiotic use during the lifetime, which would restrict the donor pool even further and result in an even less generalizable sample of donors and biome profiles.(Woodworth, Carpentieri, Sitchenko, & Kraft, 2017) However this issue was not raised during the qualitative interviews, possibly due to the respondent's positive perspectives on FMT.

As mentioned previously in the Key Informant Interview methods, generally no less than fifteen interviews is considered sufficient in qualitative research, regardless of the discipline. In this research, only four (4) interviews were conducted; therefore, the results are not valid as the sample size is not sufficient to support any meaningful conclusions. If less than fifteen interviews were used, it would be a substantial threat to the construct validity of the findings. As with all qualitative studies, there is the potential for research bias, especially because in this case, FMT is a topic that fascinated me. To reduce

potential researcher bias, I used strategies such as triangulation of ideas, searching for negative case findings, and using audit tools such as the semi-structured interview protocol and recording interviews.

Lastly, for the development of the model and interpretation of results, there are several limitations to consider. The model may have been better served using microsimulation or another structure in a more robust modeling software that had larger than an economic focus. Regarding threats to construct validity, the construction of the model, selection of variables and ranges, and assumptions contained within could be made incorrectly and threaten the overall integrity and validity of the model; for example, adverse events and ongoing costs of care for follow-up treatment could have been included in the model development to develop a more robust model. The model and variable estimates within were constructed using the best possible evidence, including the most recent evidence-based treatment guidelines and their supporting evidence bases, and sensitivity analyses were conducted to test the thresholds and limitations of the model. Validation of model results was not conducted; however, a more robust model should be minimally validated by expert opinion and ideally, tested against actual results. Last, threats to statistical validity such as inappropriate use of statistical techniques, use of a statistical test lacking sufficient power, and mistaking a trivial effect for support for the research hypothesis could be potential risks. The economic modeling software contains some troubleshooting features that do not permit the model to run if certain criteria for the model to perform are not met, for instance if probabilities do not sum to 1. Additionally, the model inputs were generated from a rigorous review of the literature, and conservative estimates were selected and further tested during sensitivity analysis. However further model testing, training, and validation is needed in future studies. Approaches like threshold testing in which the threshold at which the cost and efficacy of standard antibiotic therapies would become obsolete could be explored to test the validity of the

conclusions drawn from the model. If future methodological approaches include machine learning techniques, traditional validation methods like ten-fold cross validation could be used..

Future Research

More research is needed to continue to explore the impact of policy and regulations, like the classification and use of stool or the lack of accounting for externalities such as antibiotic resistance, on both individuals and the population. There is a dire need to incorporate more evidence-based and data driven decisions into policy making and to avail policymakers to test their hypotheses through ethical means such as modeling before engaging in smaller scale pilots and demonstration programs. Likewise, the study of translational and implementation science is critically important to facilitate the spread and scaling of successful interventions and to tailor them for local success.

Specific to this research, the economic model could be expanded in complexity and scope with more robust modeling capabilities, and its application could be expanded to include additional diseases beyond CDI, as well as additional treatment options. Much additional research is needed regarding safety for dangerous pathogens, like antibiotic resistant *E. coli,* or other MDRO or novel pathogens, like SARS-CoV-2, that could be transmitted via FMT, as well as the long-term effects and distal sequalae, (e.g., affect changes) of FMT. During the course of the research, we considered modeling the impact of expanded use of FMT using synthetic data representing a population, which would be interesting and informative, but was considered too time consuming and out of scope. Future research could explore the use of synthetic population data to explore the conditions at which FMT becomes a viable first line therapy and the threshold at which the threat or practicality of antibiotic resistance overtakes traditional antibiotic therapies.

Conclusion

FMT and microbiota therapy are promising novel treatment options that will likely become more widely used as understanding of the role of the microbiome in the immune system grows and as the need for non-antibiotic therapies increases. More research is needed on the safety and efficacy of FMT, including into unintended and long-term effects, for various ailments before widespread adoption of FMT. The current regulatory framework is not flexible enough to adapt to the rapid advances in innovative technology and treatment options, and the economic implications of failing to account for risk of antibiotic resistance and declining efficacy of antibiotics in the future requires rapid advances in innovative technology and treatment options.

Over the course of this research, the research and practice landscape evolved rapidly, and more advances and discoveries are certain to come. It is an exciting time full of possibility and hope that we can reduce or eliminate some of the suffering causes by treatment-resistant diarrhea, such as CDI, and other gut biome mediated illness and conditions. As technology and science rapidly evolve, we, as researchers, practitioners, and policy-makers, must balance the need for more and better data, the potential for unintended consequences, and the unknown unknowns while striving to make life-saving treatment available and accessible to as many people as possible.

APPENDIX A. SUMMARIES OF INCLUDED ARTICLES FOR POLICY REVIEW

Costello, 2019(S. P. Costello & Bryant, 2019)
Faecal microbiota transplantation in Australia: bogged down in regulatory uncertainty

Article Type	Editorial/Commentary
Summary/Key Points	This article provides a brief review of the evidence for FMT and the currently regulatory status in Australia. In Australia, FMT and stool are not neatly classified under the current regulatory framework provided by the Therapeutic Goods Association (TGA). The authors propose a "bespoke" regulatory framework for FMT and stool that would ensure the following: a focus on safety of the product rather than standardization (and compliance with cGMP), nationally agreed and endorsed screening and manufacturing standards for production of FMT product, national distribution from stool banks who have agreed to abide by the standards, and equitable access to timely, safe, cost effective FMT in Australia.

Costello, 2017(S. Costello, Van der Poorten, & Andrews, 2017)
Fecal microbiota transplantation for recurrent Clostridium difficile infection: When regulatory affairs do not keep pace with evidence-based medicine

Article Type	Editorial/Commentary
Summary/Key Points	FMT in Australia has "uncertain regulatory status" and is currently defined as a drug; however, stool is not listed on the country's drug registry. FMT is not regulated by condition and FMT preparation must be done by the physician administering the stool. The authors comment that the regulatory environment poses two main challenges: lack of oversight and logistical barriers to procurement and delivery. The authors pose that increasing access to FMT via clarification of regulatory guidance and oversight, as well as the use of stool banks would increase access within the public healthcare system and provide protections for patients.

Edelstein 2016(C. Edelstein, Daw, & Kassam, 2016)
Seeking safe stool: Canada needs a universal donor model

Article Type	Original Research: Regulatory Opinion
Summary/Key Points	The article summarizes the regulatory frameworks that could and do govern stool and FMT and review the challenges of regulation including biologic complexity, intellectual property, as well as manufacturing, market competition, & procurement/supply chain management (e.g. stool banks). The authors review the current state of regulation for FMT and stool in the US, Canada, Australia, Europe, and China. The authors conclude that any long-term solution should promote safe access to FMT.

Edelstein, Kassam 2015(C. A. Edelstein, Kassam, Daw, Smith, & Kelly, 2015)
The regulation of fecal microbiota for transplantation: an international perspective for policy and public health

Article Type	Editorial/Commentary

Summary/Key Points	In this commentary, the authors advocate for a centralized stool bank donor model in Canada, rather than a directed donor model, which puts the onus and burden for identification, screening (and re-screening), monitoring, and reporting on the provider and patient in a decentralized model. The authors compare directed donor versus centralized stool bank options in regard to safety, access, and cost.

Hoffman, 2017(D. Hoffmann et al., 2017)
Improving regulation of microbiota transplants

Article Type	Original Research
Summary/Key Points	In this article, the authors present a revised improved regulatory approach for screening of stool for FMT and oversight of stool banks with the purpose of ensuring safe access to FMT as a therapy. The revised approach is a product of discussions from a U.S. based workgroup/panel of experts convened to explore regulatory pathways for microbiota therapies.

Hoffman 2017(D. E. Hoffmann et al., 2017)
A proposed definition of microbiota transplantation for regulatory purposes

Article Type	Editorial/Commentary
Summary/Key Points	The article is a summary of the discussion from convening an NIH-funded Working Group to discuss “Microbiota Transplantation: Recommendations for a Regulatory Framework” and a consensus definition for microbiota transplant. Microbiota transplantation was defined as: "A microbiota transplantation is the transfer of biologic material containing a minimally manipulated community of microorganisms from a human donor to a human recipient (including autologous use) with the intent of affecting the microbiota of the recipient." There is considerable discussion of the mechanisms, features, and regulatory considerations for the range of "manipulated" microorganisms.

Hvas, 2020(Hvas et al., 2020)
Faecal microbiota transplantation: A life-saving therapy challenged by commercial claims for exclusivity

Article Type	Editorial/Commentary
Summary/Key Points	In the article, the authors call for regulatory categorization of FMT and stool as a tissue, even though both are considered exempt by the European Tissue and Cells Directive (EUTCD 2004/23/ec). However the author argues that FMT and stool are more comparable to a tissue and that the legal basis for regulation as a tissue provides standards for donation, procurement, testing, processing, preservation, storage, and distribution of the product. The author also argues that classifying and regulating FMT and stool as a tissue, rather than drug, would provide more access to the treatment as it would prevent claims of exclusivity as are allowed with drugs by pharmaceutical manufacturers. The authors participate in a hospital-based stool bank in Denmark.

Jørgensen, 2019(Jørgensen et al., 2019)
Banking feces: a new frontier for public blood banks?

Article Type	Review
Summary/Key Points	In this article, the authors summarize the important components needed to operate a stool donation system and discuss the regulatory challenges that have faced FMT. The authors acknowledge a growing European consensus to regulate stool and FMT as a tissue, but argue the category may be too narrow given the dynamic nature of the product. The authors state that an IND system for new drugs, like in the US, would not lend itself to being applied in a Scandinavian medical system in which hospitals are public and treatments are free. The authors argue that adopting the infrastructure and framework for blood donation would allow quick, efficient, and equitable access to FMT in Denmark and globally.

Keller, 2020(Keller, Ooijevaar, et al., 2020)
A standardised model for stool banking for faecal microbiota transplantation: a consensus report from a multidisciplinary UEG working group

Article Type	Original Research
Summary/Key Points	This document is a consensus document for the operation of stool banks in the EU, based on practice recommendations from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and by the Infectious Diseases Society of America (IDSA) and the quality and safety guide for tissues and cells for human application of the European Council. The authors specifically address the classification and regulation of FMT and endorse that it be regarded as a substance of human origin and thus considered equal to tissue. The document also specifically addresses standards for stool bank operations and recommends that regulatory distinction be made between the regulation of FMT versus stool banks.

Keller, 2020(Keller, Vehreschild, et al., 2020)
Donated stool for faecal microbiota transplantation is not a drug, but guidance and regulation are needed

Article Type	Editorial/Commentary
Summary/Key Points	The authors respond to calls for FMT and stool to be regulated as a transplantation product, dispute that FMT and stool should be considered a drug, and argue that FMT and stool are of human origin, despite that the active ingredients are not of human nature.

Khoruts, 2019(Alexander Khoruts, Hoffmann, Palumbo, Rothstein, & Knoppers, 2019)
The Impact of Regulatory Policies on the Future of Fecal Microbiota Transplantation

Article Type	Original Research
Summary/Key Points	This article describes and explores two possible scenarios in which FMT becomes unavailable—the first in which a newly approved microbiota-based drug is developed and usurps FMT in use, and the second in which the FDA in the US no longer permits the sale of products now sold and distributed by stool banks. In this discussion, the authors discuss the regulatory challenges

	and history in the US-context, as well as possible future outcomes. The authors note that the FDA has classified stool and FMT as a biologic product and as such falls under the regulatory purview of drugs. The authors also discuss financial implications of classification of FMT as a drug, including any future therapeutics developed to treat rCDI as being offered regulatory and financial protections under Orphan Drug status, Breakthrough Therapy Designation, or both.

Labuschaigne, 2020(Labuschaigne et al., 2020)
The ethicolegal framework relevant to human faecal microbiota transplants in South Africa: Parts 1-3

Article Type	Original Research
Summary/Key Points	In this three-part article, the authors review and discuss the classification of FMT and stool for regulatory purposes in South Africa. The authors argue that stool and FMT should be regulated as human tissue in terms of the South African National Health Act 61 of 2003, and argues that stool banks should be regulated as tissue banks. In the three-part series, the authors review and discuss current evidence for FMT and its use to treat CDI. FMT is currently only being used in a small number of research cases in South Africa and the author argues for early adoption of a legal framework for regulation to avoid the legal and regulation challenges faced in other countries.

Lagier 2014(Lagier, 2014)
Faecal microbiota transplantation: from practice to legislation before considering industrialization

Article Type	Review
Summary/Key Points	This article summarizes the current state of FMT research and use, including the regulations in the US, UK, France, and other European countries. The author reviews the various ways that FMT is screened and delivered, including second generation preparations like pills.

Lin, 2019(Lin, Hung, Ko, & Ruan, 2019)
Fecal microbiota transplantation for Clostridium difficile infection in Taiwan: Establishment and implementation

Article Type	Original Research
Summary/Key Points	In this article, the authors provide guidance and instruction for hospitals implementing an FMT program in concert with Taiwan Microbiota Consortium and Taiwan FMT Expert Consensus. In addition, the authors directly address the global lack of consensus for categorization and regulation of stool and FMT. In Taiwan, the Taiwan Microbiota Consortium has recommended FMT for years and has focused consensus for regulation on indications for transplantation, eligible centers and FMT team members, donor selection, fecal processing and delivery, and post-FMT patient monitoring, rather than the classification of the product.

Ma 2017(Yonghui Ma, Jiayu Liu, Catherine Rhodes, Yongzhan Nie, & Faming Zhang, 2017)

Ethical Issues in Fecal Microbiota Transplantation in Practice

Article Type	Review
Summary/Key Points	This article summarizes the current state of FMT research and describes a comprehensive review of the "ethical, social, and regulatory implications" of its use. The authors take a global perspective to identify and discuss "five areas of major ethical and social implications: (1) informed consent and the vulnerability of patients; (2) determining what a “suitable healthy donor” is; (3) safety and risk of FMT; (4) commercialization and potential exploitation of vulnerable patients; and (5) public health implications." The authors conclude that there is currently an ethical imperative to make safe and accessible FMT available for people for whom "alternative treatments have failed."

Megerlin 2014(Megerlin & Fouassier, 2014)
Faecal microbiota transplantation in France: what applicable law?

Article Type	Review
Summary/Key Points	The article reviews the legal argument for classifying stool a *sui generic* substance. The article reviews key passages in the French Public Health and Civil Codes and walks through the logic of stool & FMT being supported or refuted in the passage. It is a detailed look at the regulation and legislation impacting the use of FMT and stool in France.

Mullish 2015(Mullish & Williams, 2015)
Obstacles to establishing an NHS faecal transplant programme

Article Type	Editorial/Commentary
Summary/Key Points	In this editorial response article, the authors comment on the cost of screening stool donors, the lack of clarity in regard to if FMT and stool are governed under "microbiology, gastroenterology, or pharmacy" regulations, and logistical barriers to access to FMT for patients, including supply chain management.

Ossorio, 2019(Ossorio & Zhou, 2019)
FMT and Microbial Medical Products: Generating High-Quality Evidence through Good Governance

Article Type	Original Research
Summary/Key Points	In this article, the authors present that FMT has low quality evidence, then discuss regulatory challenges in the US to developing higher-quality more robust scientific evidence by incentivizing well designed RCTs to test stool and stool derived microbial products. The authors describe regulatory historical challenges in the US in the regulation of FMT, stool, and stool banks. Last, the authors provide a proposal for governing FMT and stool-derived microbial products which requires change in the FDA enforcement discretion of stool banks, but not underlying changes in the statutes or regulations.

Sachs, Edelstein 2015(Sachs & Edelstein, 2015)

Ensuring the safe and effective FDA regulation of fecal microbiota transplantation

Article Type	Review
Summary/Key Points	The article reviews the FDA decision to regulate stool as a biologic drug and argues that the approach is both over and under regulatory. The authors cite the laws under which FMT and stool can be regulated, and describe & evaluate the current versus alternative policy decisions. The article provides a legal and scientific review of the issues scientific complexity, the FDA's role in drug/brand exclusivity and use of enforcement discretion, and safety concerns. The paper reviews existing regulatory paradigms that may apply to FMT and stool including blood, tissue which includes cord blood, drugs, and enforcement discretion.

Salman 2016(Salman et al., 2016)
FMT happens: Regulating fecal microbiota therapy in Canada; What you need to know

Article Type	Review
Summary/Key Points	The article reviews Health Canada's policy on regulating FMT and stool as a biologic drug. The authors assert that "absence of consensus" for preparation and administration of FMT is a contributor to the lack of regulatory clarity in Canada. In 2012, a working group recommended that stool be classified as "a new biological drug, thus requiring a clinical trial application (CTA) by clinicians." In 2015, Health Canada issued its first policy (not legislative) statement reiterating classification as a new biological treatment. Like the US, Canada allows application of FMT without a clinical trial application for CDI "not responsive to conventional therapies", which was clarified shortly afterwards in August 2015 in the "FMT Guidance Document". The FMT Guidance Document does not specify preparation and administration methods "as a condition for its exemption of clinical trial requirements." In addition, new biologic drugs are subject to more rigorous standards than new drugs, "as the former category requires additional chemical analysis and manufacturing information to ensure purity and quality" which may be problematic for stool in the future. While Health Canada's policies and regulations do not specify that CDI must be "recurrent", in other ways, they are designed to closely align with those of the US; of note, "unresponsive to conventional therapies" in Canada is considered after two failed rounds of antibiotics, rather than three in the US. The article also briefly reviews informed consent and post-event surveillance practices in Canada, both of which the authors caution may not be sufficiently considered for the new practice of FMT.

Scheeler, 2019(Alexandra Scheeler, Hoffmann, Rothstein, & Knoppers, 2019)
Where Stool is a Drug: International Approaches to Regulating the use of Fecal Microbiota for Transplantation

Article Type	Original Research
Summary/Key Points	This article provides a discussion of the various frameworks and rationales used to regulate stool, and then summarizes the current regulatory status of

	FMT and stool from 75 countries and three Special Administrative Regions globally.

Smith 2014(Smith, Kassam, Edelstein, Burgess, & Alm, 2014)
OpenBiome remains open to serve the medical community

Article Type	Editorial/Commentary
Summary/Key Points	The purpose of this article is to clarify that Open Biome is still open after the FDA decision to regulate FMT & stool as a drug, except for compassionate use for *c. diff*. However, in the conclusion, the authors pose that the safety of FMT could be improved by the institution of policy "instituting mandatory minimum screening requirements for all FMT donors."

Terveer, 2017(Terveer et al., 2017)
How to: Establish and run a stool bank

Article Type	Original Research
Summary/Key Points	This article provides details the 2015 founding of the Netherlands Donor Feces Bank (NDFB) and provides the standard operation procedures used within for donor recruitment, donor selection, donor screening, and production, storage, and distribution of frozen fecal product for FMT. As there was not consensus regarding the legislative aspect of stool and FMT, the authors provide an overview of the number of stool banks in operation globally and relevant legislation pertaining to operations, manufacturing, and distribution. The authors provide operational and business cost data on starting a stool bank in the Netherlands.

Verbeke, 2017(Verbeke, Janssens, Wynendaele, & De Spiegeleer, 2017)
Faecal microbiota transplantation: a regulatory hurdle?

Article Type	Original Research
Summary/Key Points	This article calls for a pragmatic and balanced approach to regulating FMT and stool in the European Union. The article summarizes current regulatory challenges and approaches proposed and in use globally, as well as work in the EU on the topic. The authors call for FMT to be regulated under the authority and domain of European Advanced Therapy Medicinal Products, as it offers flexibility that answers the authors' calls for pragmatism. The authors pose seven principles to be considered for FMT regulation: regulatory harmonization; patient empowerment, quality; donor anonymity; efficacy; information; and pharmacovigilance.

Vyas 2015(Vyas, Aekka, & Vyas, 2015)
Fecal transplant policy and legislation

Article Type	Editorial/Commentary
Summary/Key Points	This article reviews stool and FMT classification as a drug from a policy perspective. The authors argue that stool and FMT, if classified as a tissue, would increase safe access to treatment. They also pose that the introduction of good manufacturing practice guidelines would ensure the

	safety, reliability, and oversight necessary for this treatment while improving supply chain management.

APPENDIX B. IRB DECISION LETTER

FWA #00000287

Institutional Review Board Office

615 N. Wolfe Street / Room E1100
Baltimore, Maryland 21205-2179
Phone: 410-955-3193
Toll Free: 1-888-262-3242
Fax: 410-502-0584
Email: jhsph.irboffice@jhu.edu
Website: www.jhsph.edu/irb

NOT HUMAN SUBJECTS RESEARCH DETERMINATION NOTICE STUDENT PROJECTS

Date: May 3, 2016

To: Nichole Persing

Re: **DrPH Dissertation Student Project Title:** "The Shitty Dissertation: An Economic & Policy Analysis of Expanding the Use of Fecal Microbiota Transplant"

The JHSPH IRB reviewed the IRB Office Determination Request Form for Primary (New) Data Collection (received 4/28/16) on **May 3, 2016**. We have determined that the proposed activity described in your request form will involve subjects who are key informants and collects expert opinions and judgments designed to elicit information from them in their professional capacity about the issues surrounding the use of fecal transplants, including policy and economic issues. No personal or private information about informants will be collected. Thus, the proposed activity does not qualify as human subjects research as defined by DHHS regulations 45 CFR 46.102, and does not require IRB oversight.

We anticipate that you will follow ethical practices in your interactions with individuals in the community during the course of your project. You are responsible for notifying the JHSPH IRB of any future changes that might involve human subjects and require IRB review.

If you have any questions regarding this determination, please contact the JHSPH IRB Office at (410) 955-3193 or via email at jhsph.irboffice@jhu.edu.

/teb

cc Douglas Hough, PhD
Faculty Advisor / Associate Scientist
Department of Health Policy and Management
Johns Hopkins University Bloomberg School of Public Health

APPENDIX C. SEMI STRUCTURED INTERVIEWING PROTOCOL

Semi Structured Interviewing Protocol–WITH AUDIOTAPING

For Key Informant Interviews

An Economic & Policy Analysis of Expanding the Use of Fecal Microbiota Transplant

1. Hello & introduction
2. Review Oral Consent Waiver
3. Semi Structured Interview Questions

Background

1. Tell me a little about your background
2. Can you tell me about your experience with fecal transplants and how you got interested in this topic area?

Pros & Cons

1. What are the biggest benefits to fecal transplant use? What are the biggest advantages to expanding?
2. What are the biggest harms/unintended consequences to fecal transplant use? What are the biggest barriers to current use? To expanding use?

Future Considerations

1. Where do you foresee opportunities for expanding use of fecal transplant? [Populations, disease states, etc.]
2. What would you like to see happen next in the [fecal transplant] field--operationally or research?
3. Imagine here we are 5 years 10 years down the road. FMT has been a total mess, crashed & burned. What happened?

Final Thoughts

1. What else do you want people to know about fecal transplant? If you could tell people only 1 thing about fecal transplant, what would it be?
2. Is there anyone else you recommend that I talk to or resources that I should know about?

Thank you

Thank you for your time and participation in this interview. The information that you provided to us will be very helpful in this project. Please feel free to contact me if you have any additional thoughts, questions, or concerns.

APPENDIX D. INFORMED CONSENT SCRIPT

CONSENT FORM – INTERVIEW WITH AUDIOTAPING

Consent to Participate in Research (*Key Informant Interviews)*
An Economic & Policy Analysis of Expanding the Use of Fecal Microbiota Transplant

Introduction and Purpose
My name is Nichole Persing. I am a graduate student at the Johns Hopkins School of Public Health working with my faculty advisor, Professor Doug Hough in the Department of Health Policy & Management. I would like to invite you to take part in my research study, which concerns expanding use of fecal transplants and the economic & policy implications, using treatment of *c. diff* as a case study.

Procedures
If you agree to participate in my research, I will conduct an interview with you at a time and location of your choice. The interview will involve questions about the issues surrounding the use of fecal transplants. It should last between 30-60 minutes. With your permission, I will audiotape and take notes during the interview. The recording is to accurately record the information you provide, and will be used for transcription purposes. If you choose not to be audiotaped, I will take notes instead. If you agree to being audiotaped but feel uncomfortable at any time during the interview, I can turn off the recorder at your request. If—at any point-- you don't wish to continue, you can stop the interview at any time.

I expect to conduct only one interview; however, follow-ups may be needed for added clarification. If so, I will contact you by email/phone to request clarification.

Benefits
There is no direct benefit to you from taking part in this study. It is hoped that the research will help inform future discussions and research on the economic and health policy impacts regarding the use of fecal transplants.

Risks/Discomforts
Some of the research questions may make you uncomfortable or upset. You are free to decline to answer any questions you don't wish to, or to stop the interview at any time. As with all research, there is a chance that confidentiality could be compromised; however, we are taking precautions to minimize this risk.

Confidentiality
Your study data will be handled as confidentially as possible. To minimize the risks to confidentiality, we will limit access to study records and securely store the study data in password protected computer systems and locked file cabinets. If results of this study are published or presented, individual names and other personally identifiable information will not be used unless you give explicit permission. Subjects will be asked for oral rather than signed consent.

When the research is completed, I may save the tapes and notes for use in future research done by myself or others. These records will be retained for up to 3 years after the study is over, per data retention practices required by federal organizations like the NIH or DHHS. The same measures described above will be taken to protect confidentiality of this study data.

Compensation
You will not be paid for taking part in this study.

Rights
Participation in research is completely voluntary. You are free to decline to take part in the project. You can decline to answer any questions and are free to stop taking part in the project at any time. Whether or not you choose to participate in the research and whether or not you choose to answer a question or continue participating in the project, there will be no penalty to you or loss of benefits to which you are otherwise entitled.

Questions
If you have any questions about this research, please feel free to contact me. I can be reached at 240-298-6823 nichole.persing@gmail.com or npersing@jhu.edu. Doug Hough can be reached at 410-502-2886 or Douglas.Hough@jhu.edu.

If you have any questions about your rights or treatment as a research participant in this study, please contact the Johns Hopkins Bloomberg School of Public Health's Internal Review Board via phone at 410-955-3193 or Toll-Free at 1-888-262-3242, or via e-mail JHSPH.irboffice@jhu.edu.

****

CONSENT
If you agree to participate, please say so. You will be given a copy of this form to keep for your own records.

OPTIONAL CONSENT
If you agree to allow your name or other identifying information to be included in all final reports, publications, and/or presentations resulting from this research, please say so.

APPENDIX E. MODEL INPUT VARIABLES

Variables

The following table provides the variable names, description and values for the Economic Models. The root definition shown is the base case, point estimate identified from the literature; the high and low values are used in the Sensitivity Analysis.

Table 19. Model Input Variables

Name	Description	Base Case	Low	High
c_fidaxomicin	cost of fidaxomicin per claim	3944.7	0.1	0.1
c_FMTcolonoscopy	cost of FMT via colonoscopy	5349	0.1	0.1
c_FMTenema	cost of FMT via enema	1600	100	3500
c_FMTpill	cost of FMT capsule per dose	2050	2050	6150
c_metroIV	cost of metronidazole IV	48.6	0.1	0.1
c_metroPO	cost of metro PO per claim	64.6	25	454
c_rifaximin	cost per claim of rifaximin	2156	0.1	0.1
c_vancPO	cost per claim of vancomycin	313.70	9.7	8227.7
eff_fidaxomicin	effectiveness of fidaxomicin 10d	0.88	0	0.88
eff_FMTcolonoscopy	effectiveness of FMT via colonoscopy	0.87	0.8	0.9999
eff_FMTenema	effectiveness of FMT via enema	0.621	0	0.621
eff_FMTpill	effectiveness of FMT via pill	0.733	0.68	0.91
eff_metronidizole	effectiveness of metronidazole at 10d	0.75	0	0.75
eff_rifaximin	effectiveness of rifaximin	85%	0	0.85
eff_vanc	effectiveness of vancomycin at 10d	0.585	0.31	0.85
eff_vancpulsetaper	effectiveness of extended vancomycin pulse taper	61%	0.1	0.1
p_Death	probability of death	8.6%	0.1	0.1
p_FMTcolonoscopy	percent use of FMT colonoscopy	85%	0.1	0.1
p_FMTenema	percent use of FMT enema	5%	0.1	0.1
p_FMTpill	percent use of FMT pill	10%	0.1	0.1
p_fulminant	prevalence of fulminant CDI	2%	0.1	0.1
p_Initial_NS	Prevalence of pts with initial, non-severe CDI diagnosis	51%	0.1	0.1
p_Initial_severe	Prevalence of pts with initial, severe CDI	47%	0.1	0.1

QALY Conversion

QALYs corresponding to different utility values when Time is set to be constant (1 year) from Prieto and Sacristán, 2003 where "for utilities expressed with a level of precision of 0.05 units, the table can be used to calculate any QALY; it is sufficient simply to multiply the QALY value in the last column by the number of years in question."

Table 20. QALY Conversion table

Time (years)	Utility	QALY
1	1	1
1	0.95	0.9753
1	0.9	0.9513
1	0.85	0.928
1	0.8	0.9055
1	0.75	0.8839
1	0.7	0.8631
1	0.65	0.8434
1	0.6	0.8246
1	0.55	0.807
1	0.5	0.7906
1	0.45	0.7754
1	0.4	0.7616
1	0.35	0.7492
1	0.3	0.7382
1	0.25	0.7289
1	0.2	0.7211
1	0.15	0.715
1	0.1	0.7106
1	0.05	0.708
1	0	0.7071

Treatment Sequence, Duration, and QALY Output

The following tables provide the treatment sequence and duration calculations, as well as the corresponding QALY output, for each stage of CDI.

Sequence options that would include consecutive rounds of the same medication were dropped from the treatment algorithm (e.g., Fidaxomicin followed by vancomycin pulse taper twice).

Table 21. Non-Severe CDI Treatment Sequences, Durations, and QALYs

Initial treatment	$Time_1$ (days)	QALY (t1)	2nd treatment	$Time_2$ (days)	QALY (t2)	3rd treatment	$Time_3$ (days)	QALY (t3)	4th treatment	$Time_4$ (days)	QALY (t4)	Total Time (days)
Fidaxomicin	10	0.8760	Vancomycin	10	0.8533	Fidaxomicin	10	0.8319	FMT	5	0.8216	35
Fidaxomicin	10	0.8760	Vancomycin	10	0.8533	Vancomycin +rifaximin	30	0.7929	FMT	5	0.7840	55
Fidaxomicin	10	0.8760	Vancomycin	10	0.8533	vanc taper	60	0.7442	FMT	5	0.7372	85
Fidaxomicin	10	0.8760	Vancomycin pulse taper	60	0.7591	Fidaxomicin	10	0.7442	FMT	5	0.7372	85
Fidaxomicin	10	0.8760	Vancomycin pulse taper	60	0.7591	Vancomycin +rifaximin	30	0.7182	FMT	5	0.7125	105
Fidaxomicin	10	0.8760	Vancomycin pulse taper	60	0.7591	FMT	5	0.7515	FMT	5	0.7442	80
Fidaxomicin	10	0.8760	FMT	5	0.8645	FMT	5	0.8533	FMT	5	0.8424	25
Fidaxomicin	10	0.8760	Vancomycin	10	0.8533	FMT	5	0.8424	FMT	5	0.8319	30
FMT	5	0.8878	FMT	5	0.8760	FMT	5	0.8645				15
Metronidazole	10	0.8760	Vancomycin	10	0.8533	Fidaxomicin	10	0.8319	FMT	5	0.8216	35
Metronidazole	10	0.8760	Vancomycin	10	0.8533	Vancomycin +rifaximin	30	0.7929	FMT	5	0.7840	55
Metronidazole	10	0.8760	Vancomycin	10	0.8533	vanc taper	60	0.7442	FMT	5	0.7372	85
Metronidazole	10	0.8760	Vancomycin pulse taper	60	0.7591	Fidaxomicin	10	0.7442	FMT	5	0.7372	85
Metronidazole	10	0.8760	Vancomycin pulse taper	60	0.7591	Vancomycin +rifaximin	30	0.7182	FMT	5	0.7125	105
Metronidazole	10	0.8760	Vancomycin pulse taper	60	0.7591	FMT	5	0.7515	FMT	5	0.7442	80
Metronidazole	10	0.8760	Vancomycin	10	0.8533	FMT	5	0.8424	FMT	5	0.8319	30
Metronidazole	10	0.8760	FMT	5	0.8645	FMT	5	0.8533	FMT	5	0.8424	25
Vancomycin	10	0.8760	Fidaxomicin	10	0.8533	vanc taper	60	0.7442	FMT	5	0.7372	85
Vancomycin	10	0.8760	Fidaxomicin	10	0.8533	Vancomycin +rifaximin	30	0.7929	FMT	5	0.7840	55

Vancomycin	10	0.8760	Vancomycin pulse taper	60	0.7591	Fidaxomicin	10	0.7442	FMT	5	0.7372	85
Vancomycin	10	0.8760	Vancomycin pulse taper	60	0.7591	Vancomycin +rifaximin	30	0.7182	FMT	5	0.7125	105
Vancomycin	10	0.8760	FMT	5	0.8645	FMT	5	0.8533	FMT	5	0.8424	25
Vancomycin	10	0.8760	Vancomycin pulse taper	60	0.7591	FMT	5	0.7515	FMT	5	0.7442	80
Vancomycin	10	0.8760	Fidaxomicin	10	0.8533	FMT	5	0.8424	FMT	5	0.8319	30

Table 22. Severe CDI Treatment Sequences, Durations, and QALYs

Initial treatment	$Time_1$ (days)	QALY (t1)	2nd treatment	$Time_2$ (days)	QALY (t2)	3rd treatment	$Time_3$ (days)	QALY (t3)	4th treatment	$Time_4$ (days)	QALY (t4)	Total Time (days)
Fidaxomicin	10	0.7787	Vancomycin	10	0.7585	Fidaxomicin	10	0.7394	FMT	5	0.7303	35
Fidaxomicin	10	0.7787	Vancomycin	10	0.7585	Vancomycin + rifaximin	30	0.7047	FMT	5	0.6967	55
Fidaxomicin	10	0.7787	Vancomycin	10	0.7585	Vancomycin pulse taper	60	0.6612	FMT	5	0.6550	85
Fidaxomicin	10	0.7787	Vancomycin pulse taper	60	0.6746	Fidaxomicin	10	0.6612	FMT	5	0.6550	85
Fidaxomicin	10	0.7787	Vancomycin pulse taper	60	0.6746	Vancomycin + rifaximin	30	0.6380	FMT	5	0.6329	105
Fidaxomicin	10	0.7787	Vancomycin	10	0.7585	FMT	5	0.7488	FMT	5	0.7394	30
Fidaxomicin	10	0.7787	FMT	5	0.7684	FMT	5	0.7585	FMT	5	0.7488	25
Fidaxomicin	10	0.7787	Vancomycin pulse taper	60	0.6746	FMT	5	0.6678	FMT	5	0.6612	80
FMT	5	0.7892	FMT	5	0.7787	FMT	5	0.7684			0.7684	15
Vancomycin	10	0.7787	Fidaxomicin	10	0.7585	Vancomycin pulse taper	60	0.6612	FMT	5	0.6550	85
Vancomycin	10	0.7787	Fidaxomicin	10	0.7585	Vancomycin + rifaximin	30	0.7047	FMT	5	0.6967	55
Vancomycin	10	0.7787	Vancomycin pulse taper	60	0.6746	Fidaxomicin	10	0.6612	FMT	5	0.6550	85
Vancomycin	10	0.7787	Vancomycin pulse taper	60	0.6746	Vancomycin + rifaximin	30	0.6380	FMT	5	0.6329	105
Vancomycin	10	0.7787	FMT	5	0.7684	FMT	5	0.7585	FMT	5	0.7488	25
Vancomycin	10	0.7787	Vancomycin pulse taper	60	0.6746	FMT	5	0.6678	FMT	5	0.6612	80
Vancomycin	10	0.7787	Fidaxomicin	10	0.7585	FMT	5	0.7488	FMT	5	0.7394	30

Table 23. Fulminant CDI Treatment Sequences, Durations, and QALYs

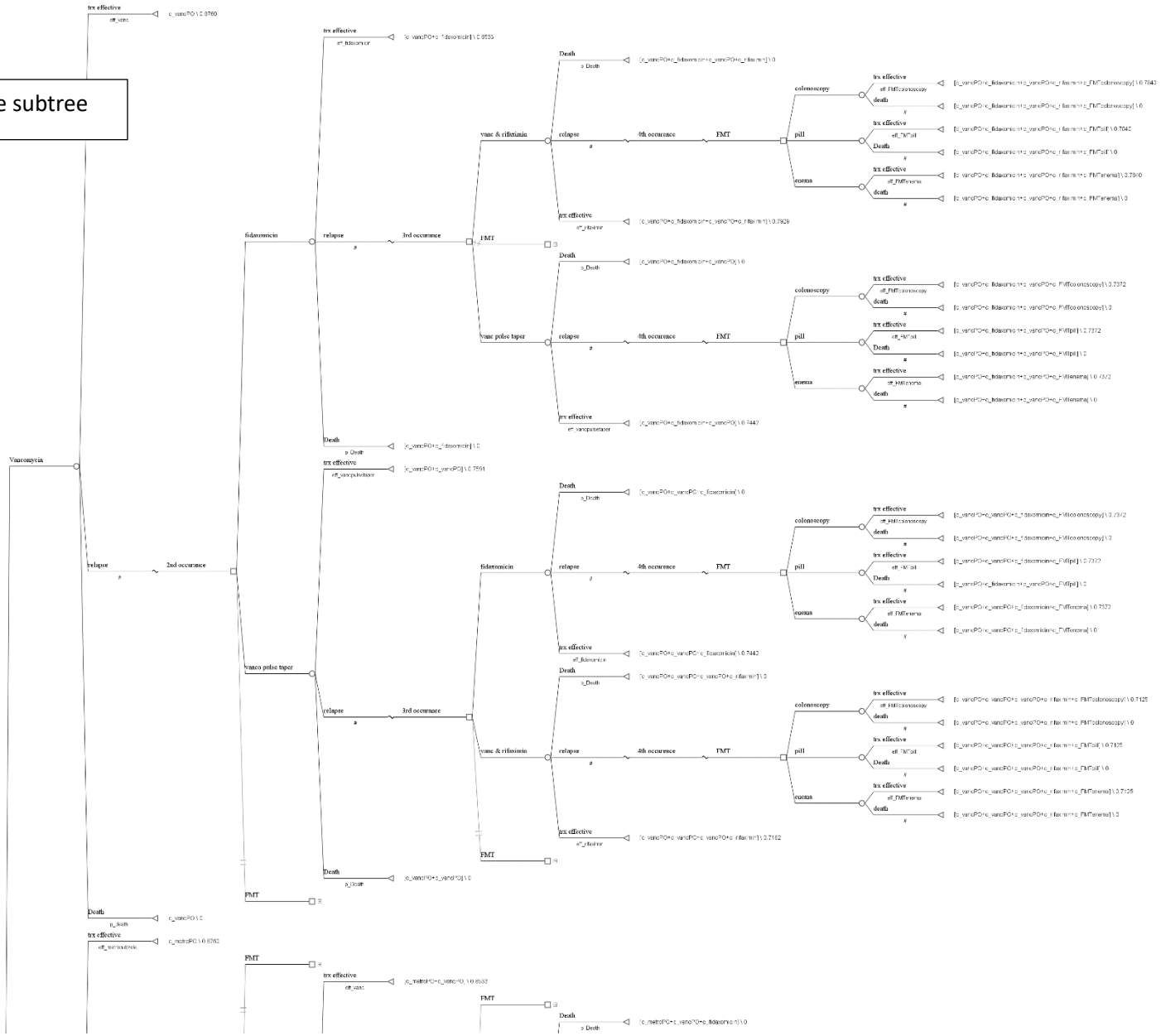
Initial treatment	**Time$_1$ (days)**	**QALY (t1)**	**2nd treatment**	**Time$_2$ (days)**	**QALY (t2)**	**3rd treatment**	**Time$_3$ (days)**	**QALY (t3)**	**4th treatment**	**Time$_4$ (days)**	**QALY (t4)**	**Total Time (days)**
FMT	5	0.6905	FMT	5	0.6814	FMT	5	0.6724			0.6724	15
Vancomycin 500 & Metronidazole IV	10	0.6814	Vancomycin pulse taper	60	0.5919	Vancomycin + rifaximin	30	0.5616	FMT	5	0.5574	105
Vancomycin 500 & Metronidazole IV	10	0.6814	Vancomycin pulse taper	60	0.5919	Fidaxomicin	10	0.5807	FMT	5	0.5755	85
Vancomycin 500 & Metronidazole IV	10	0.6814	Vancomycin pulse taper	60	0.5919	FMT	5	0.5862	FMT	5	0.5807	80
Vancomycin 500 & Metronidazole IV	10	0.6814	Fidaxomicin	10	0.6638	Vancomycin + rifaximin	30	0.6174	FMT	5	0.6107	55
Vancomycin 500 & Metronidazole IV	10	0.6814	Fidaxomicin	10	0.6638	Vancomycin pulse taper	60	0.5807	FMT	5	0.5755	85
Vancomycin 500 & Metronidazole IV	10	0.6814	FMT	5	0.6724	FMT	5	0.6638	FMT	5	0.6554	25
Vancomycin 500 & Metronidazole IV	10	0.6814	Fidaxomicin	10	0.6638	FMT	5	0.6554	FMT	5	0.6473	30

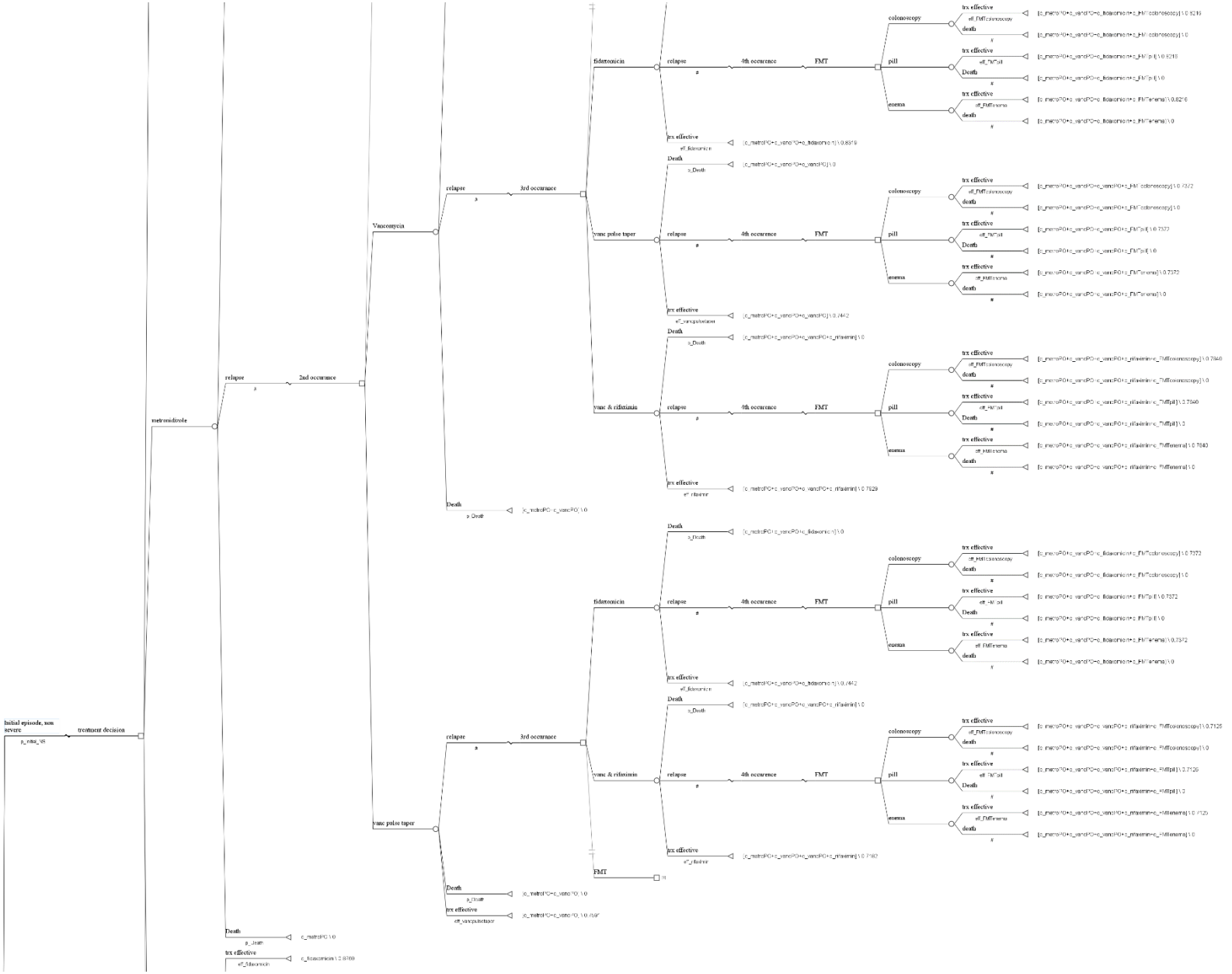
APPENDIX F. STANDARD ANTIBIOTIC TREATMENT DECISION TREE MODEL FOR CDI IN STATUS QUO SCENARIO

The three branches of the decision tree, by stage, are shown in Appendix F. The subtrees are shown as the status quo scenario without the use of FMT until after the third incidence of rCDI/ fourth episode of CDI.

1. Initial non-severe CDI subtree: Status Quo Scenario (4 pages)
2. Initial Severe CDI subtree: Status Quo Scenario (2 pages)
3. Fulminant CDI subtree: Status Quo Scenario (1 page)

Initial non severe subtree




Initial episode, non severe
p_mild_VS
treatment decision
metronidazole
relapse
#
2nd occurance
Death
p_Death
c_metroPO
trx effective
eff_fidaxomicin
c_fidaxomicin
Vancomycin
relapse
#
3rd occurance
fidaxomicin
relapse
#
4th occurance
FMT
colonoscopy
trx effective
eff_FMTcolonoscopy
death
pill
trx effective
eff_FMTpill
Death
enema
trx effective
eff_FMTenema
death
trx effective
eff_fidaxomicin
Death
p_Death
vanc pulse taper
relapse
#
4th occurance
FMT
colonoscopy
trx effective
eff_FMTcolonoscopy
death
pill
trx effective
eff_FMTpill
Death
enema
trx effective
eff_FMTenema
death
trx effective
eff_vancpulsetaper
Death
p_Death
vanc & rifaximin
relapse
#
4th occurance
FMT
colonoscopy
trx effective
eff_FMTcolonoscopy
death
pill
trx effective
eff_FMTpill
Death
enema
trx effective
eff_FMTenema
death
trx effective
eff_rifaximin
Death
p_Death
vanc pulse taper
relapse
#
3rd occurance
fidaxomicin
relapse
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4th occurance
FMT
colonoscopy
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Death
enema
trx effective
eff_FMTenema
death
trx effective
eff_fidaxomicin
Death
p_Death
vanc & rifaximin
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4th occurance
FMT
colonoscopy
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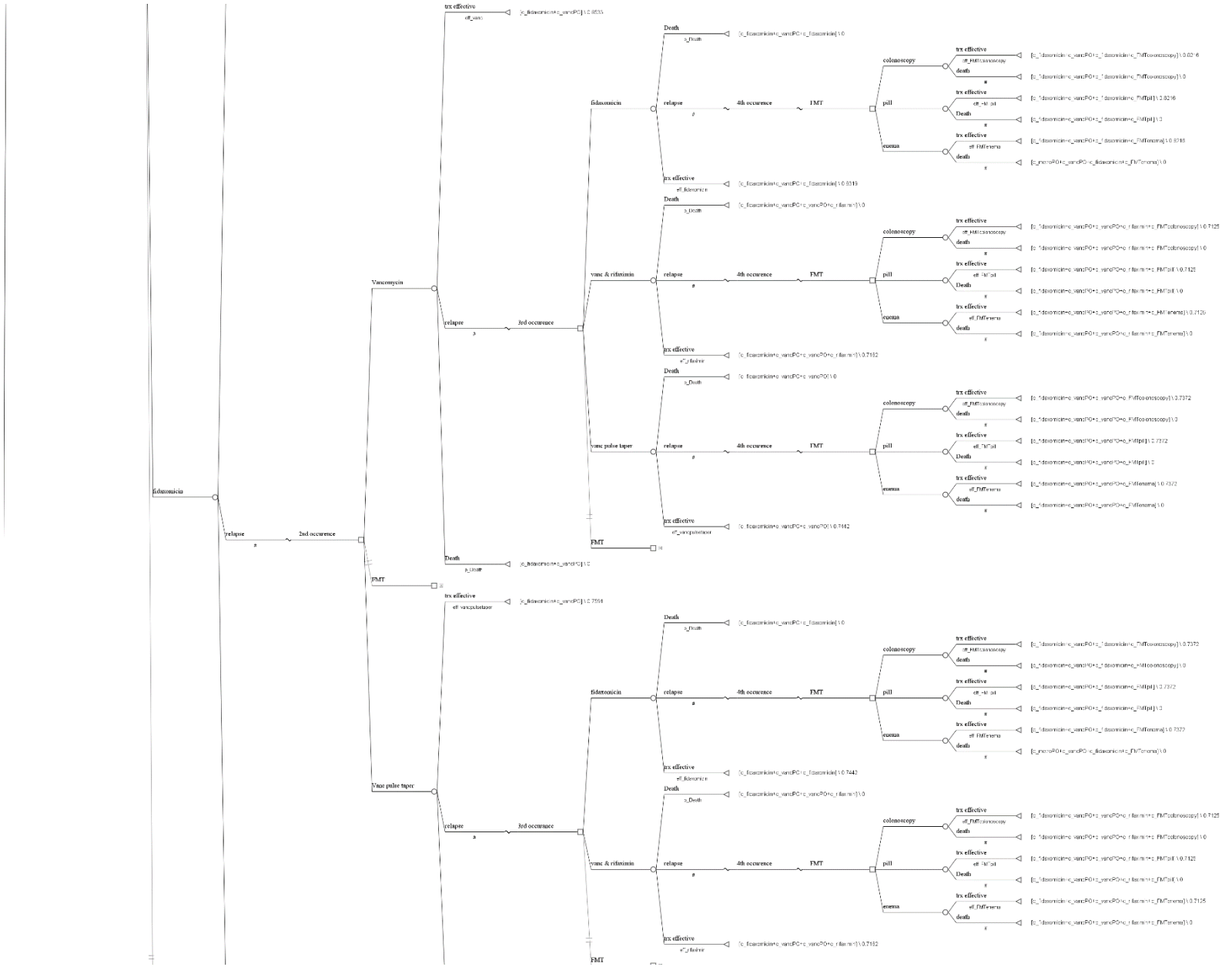
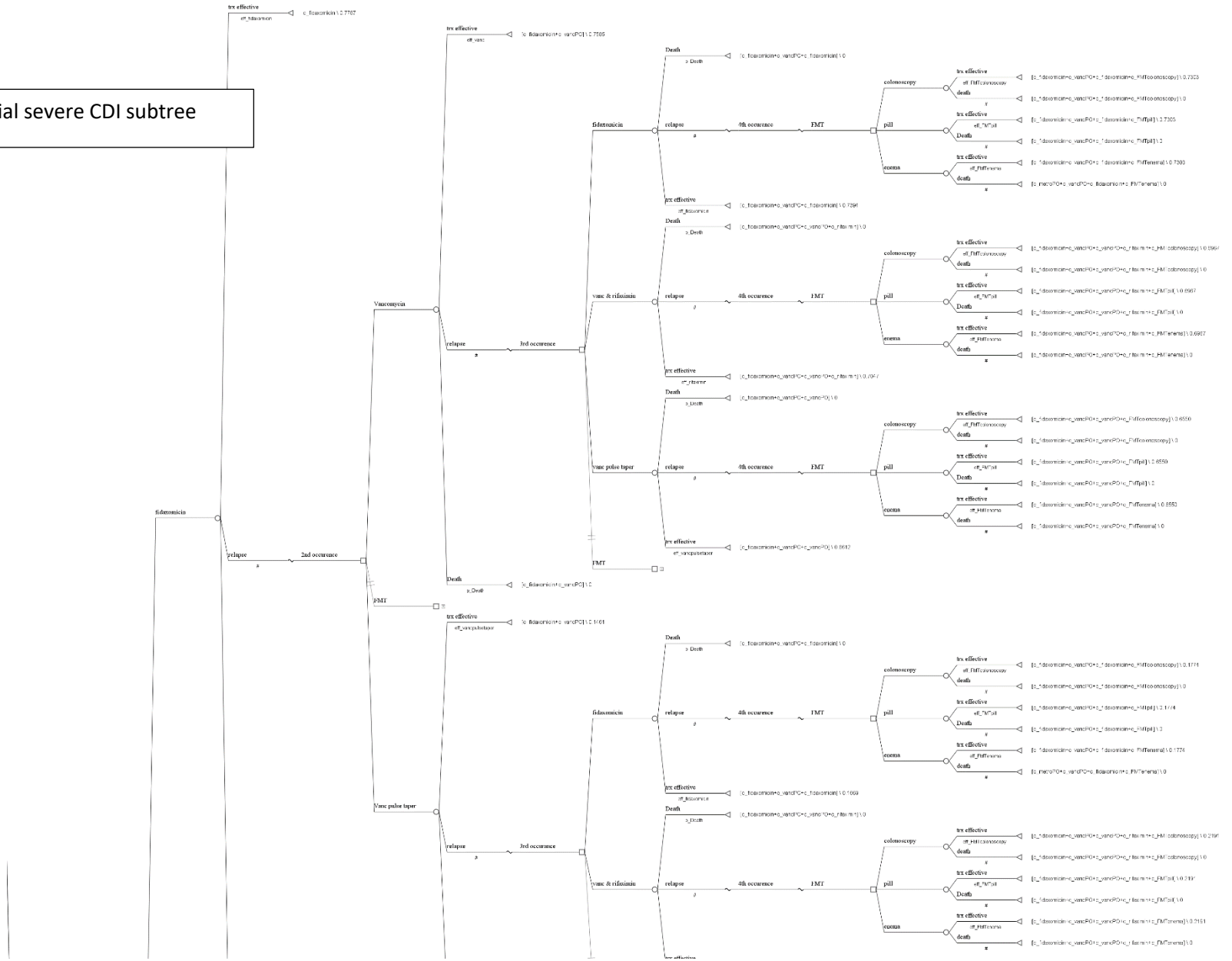
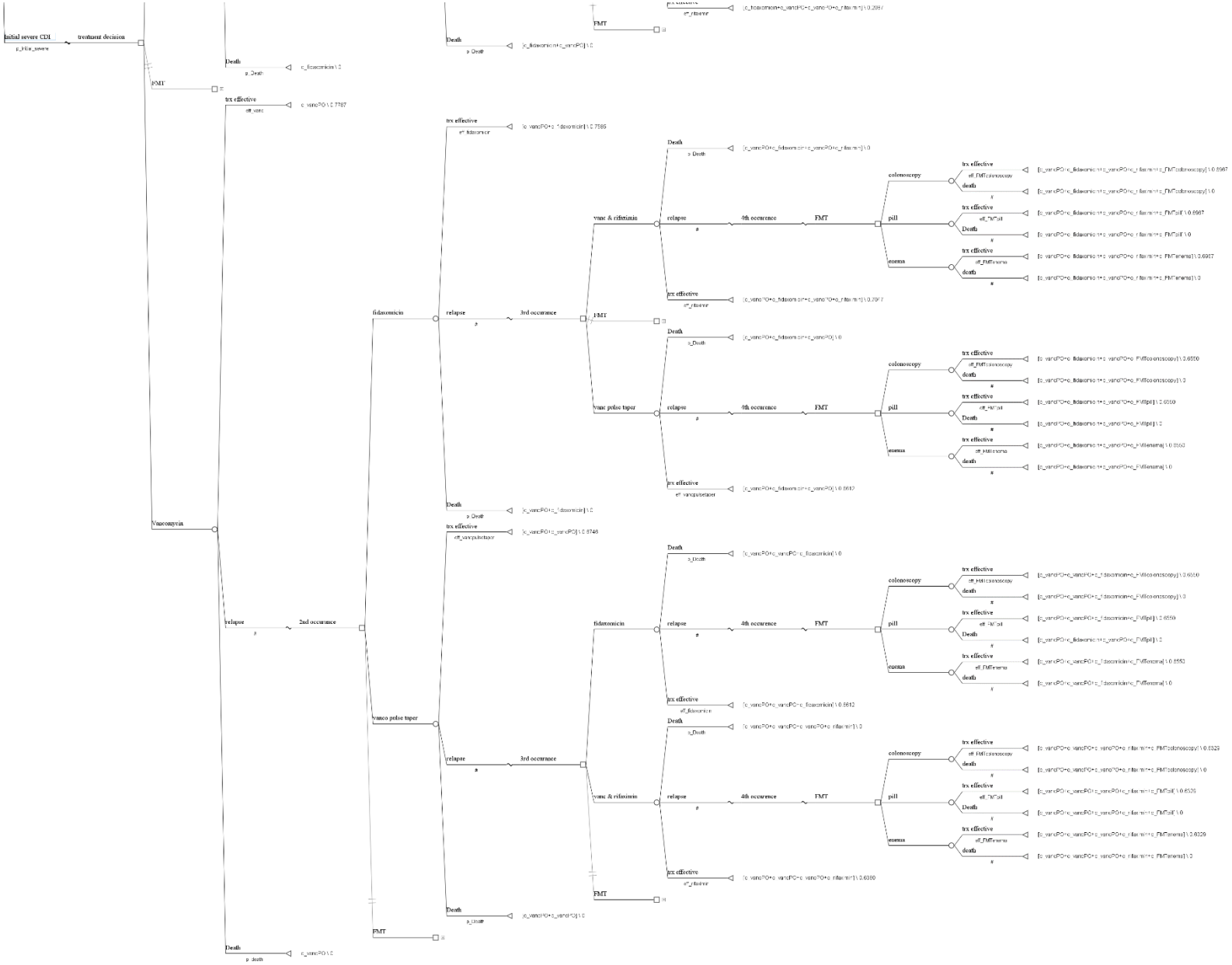
Death
p_Death
trx effective
eff_vancpulsetaper


fidaxomicin
relapse
2nd occurence
Vancomycin
relapse
3rd occurance
fidaxomicin
relapse
4th occurence
FMT
pill
colonoscopy
enema
vanc & rifaximin
vanc pulse taper
FMT
Death
trx effective
Vanc pulse taper

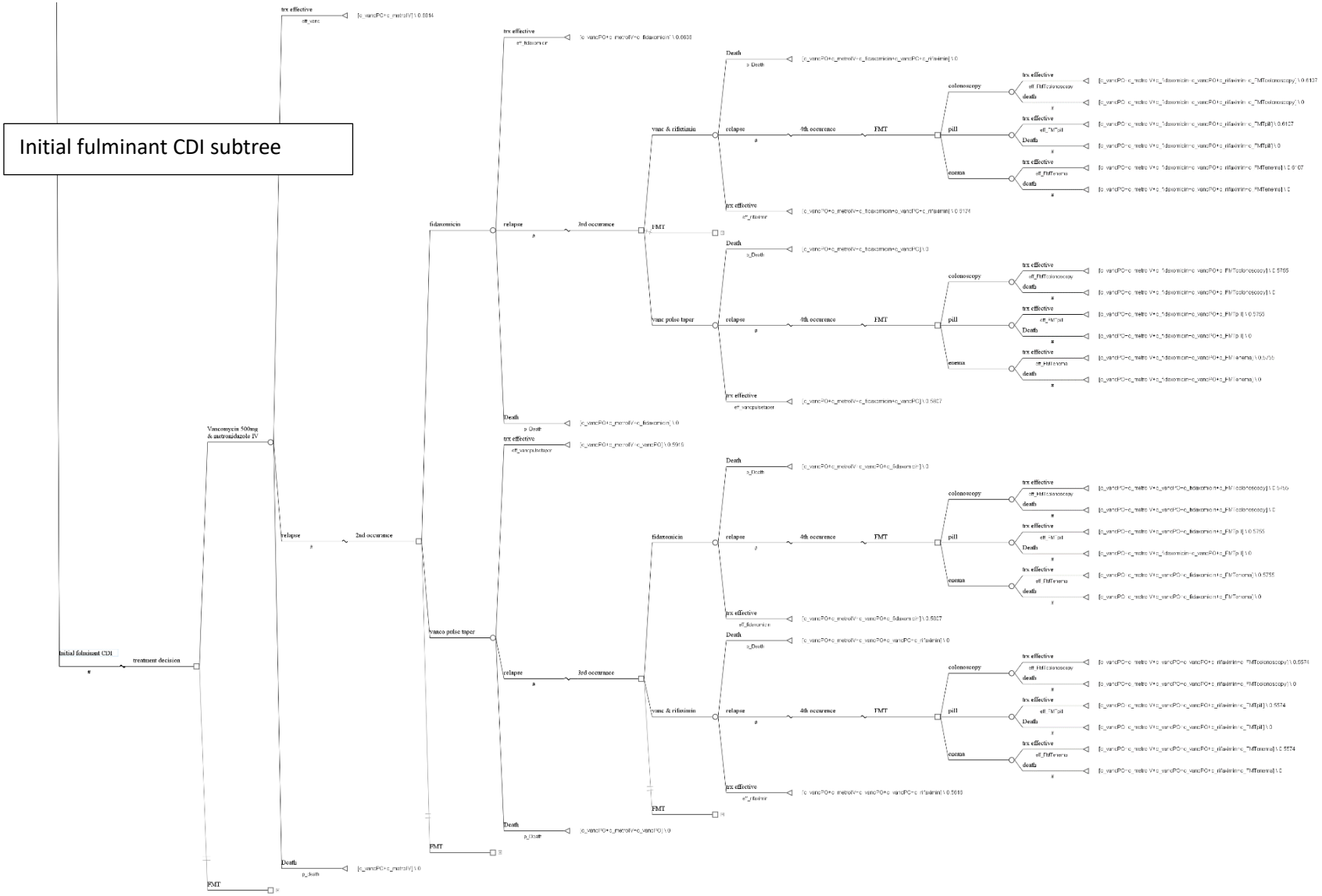

Death
Death
EMT

Initial severe CDI subtree




initial severe CDI
p_File_severe
treatment decision
Vancomycin
Death
p_Death
c_fidaxomicin \ 0
FMT
trx effective
eff_vanc
c_vancPO \ 0.7787
relapse
p
2nd occurance
fidaxomicin
trx effective
eff_fidaxomicin
[c_vancPO+c_fidaxomicin \ 0.7585
relapse
p
3rd occurance
vanc & rifaximin
Death
p_Death
[c_vancPO+c_fidaxomicin+c_vancPO+c_rifaximin] \ 0
relapse
p
4th occurance
FMT
colonoscopy
trx effective
eff_FMTcolonoscopy
death
p
[c_vancPO+c_fidaxomicin+c_vancPO+c_rifaximin+c_FMTcolonoscopy] \ 0.8987
[c_vancPO+c_fidaxomicin+c_vancPO+c_rifaximin+c_FMTcolonoscopy] \ 0
pill
trx effective
eff_FMTpill
Death
p
[c_vancPO+c_fidaxomicin+c_vancPO+c_rifaximin+c_FMTpill] \ 0.8987
[c_vancPO+c_fidaxomicin+c_vancPO+c_rifaximin+c_FMTpill] \ 0
enema
trx effective
eff_FMTenema
death
p
[c_vancPO+c_fidaxomicin+c_vancPO+c_rifaximin+c_FMTenema] \ 0.8987
[c_vancPO+c_fidaxomicin+c_vancPO+c_rifaximin+c_FMTenema] \ 0
trx effective
eff_rifaximin
[c_vancPO+c_fidaxomicin+c_vancPO+c_rifaximin] \ 0.7917
FMT
vanc pulse taper
Death
p_Death
[c_vancPO+c_fidaxomicin+c_vancPO] \ 0
relapse
p
4th occurance
FMT
colonoscopy
trx effective
eff_FMTcolonoscopy
death
p
[c_vancPO+c_fidaxomicin+c_vancPO+c_FMTcolonoscopy] \ 0.6559
[c_vancPO+c_fidaxomicin+c_vancPO+c_FMTcolonoscopy] \ 0
pill
trx effective
eff_FMTpill
Death
p
[c_vancPO+c_fidaxomicin+c_vancPO+c_FMTpill] \ 0.6559
[c_vancPO+c_fidaxomicin+c_vancPO+c_FMTpill] \ 0
enema
trx effective
eff_FMTenema
death
p
[c_vancPO+c_fidaxomicin+c_vancPO+c_FMTenema] \ 0.6563
[c_vancPO+c_fidaxomicin+c_vancPO+c_FMTenema] \ 0
trx effective
eff_vancpulsetaper
[c_vancPO+c_fidaxomicin+c_vancPO] \ 0.6612
Death
p_Death
[c_vancPO+c_fidaxomicin] \ 0
trx effective
eff_vancpulsetaper
[c_vancPO+c_vancPO] \ 0.8746
vanco pulse taper
Death
p_Death
[c_vancPO+c_vancPO+c_fidaxomicin] \ 0
relapse
p
3rd occurance
fidaxomicin
relapse
p
4th occurance
FMT
colonoscopy
trx effective
eff_FMTcolonoscopy
death
p
[c_vancPO+c_fidaxomicin+c_vancPO+c_FMTcolonoscopy] \ 0.6559
[c_vancPO+c_fidaxomicin+c_vancPO+c_FMTcolonoscopy] \ 0
pill
trx effective
eff_FMTpill
Death
p
[c_vancPO+c_fidaxomicin+c_vancPO+c_FMTpill] \ 0.6559
[c_vancPO+c_fidaxomicin+c_vancPO+c_FMTpill] \ 0
enema
trx effective
eff_FMTenema
death
p
[c_vancPO+c_fidaxomicin+c_vancPO+c_FMTenema] \ 0.6563
[c_vancPO+c_fidaxomicin+c_vancPO+c_FMTenema] \ 0
trx effective
eff_fidaxomicin
[c_vancPO+c_vancPO+c_fidaxomicin] \ 0.6612
vanc & rifaximin
Death
p_Death
[c_vancPO+c_vancPO+c_rifaximin] \ 0
relapse
p
4th occurance
FMT
colonoscopy
trx effective
eff_FMTcolonoscopy
death
p
[c_vancPO+c_vancPO+c_rifaximin+c_FMTcolonoscopy] \ 0.6329
[c_vancPO+c_vancPO+c_rifaximin+c_FMTcolonoscopy] \ 0
pill
trx effective
eff_FMTpill
Death
p
[c_vancPO+c_vancPO+c_rifaximin+c_FMTpill] \ 0.6329
[c_vancPO+c_vancPO+c_rifaximin+c_FMTpill] \ 0
enema
trx effective
eff_FMTenema
death
p
[c_vancPO+c_vancPO+c_rifaximin+c_FMTenema] \ 0.6329
[c_vancPO+c_vancPO+c_rifaximin+c_FMTenema] \ 0
trx effective
eff_rifaximin
[c_vancPO+c_vancPO+c_rifaximin] \ 0.6350
FMT
Death
p_Death
[c_vancPO+c_vancPO] \ 0
FMT
Death
p_death
c_vancPO \ 0

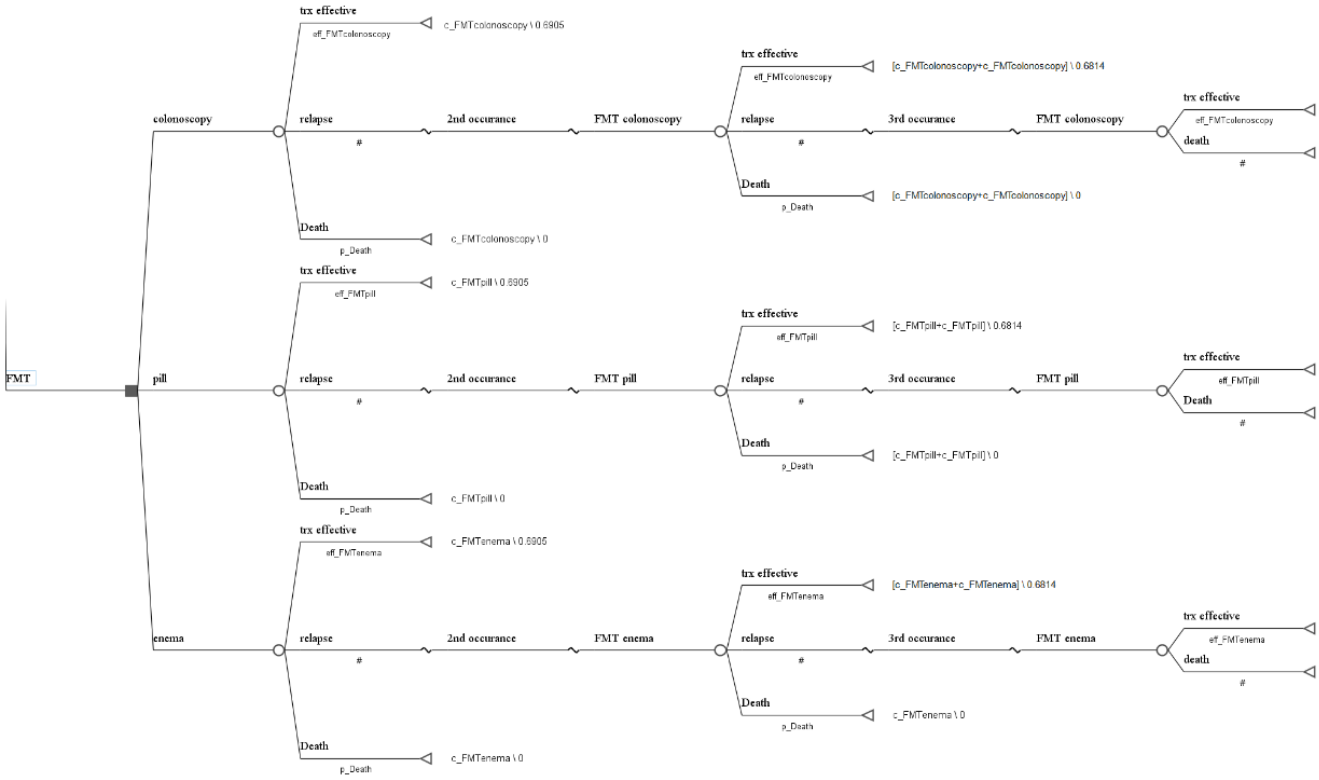
Initial fulminant CDI subtree



APPENDIX G. FMT DECISION TREE FOR ALTERNATIVE SCENARIOS

The figure below is an example of the FMT decision trees used; in the example shown, FMT is the treatment option for the initial episode of severe, fulminant CDI with all subsequent treatment options set as FMT.

Figure 16. FMT Decision Tree



APPENDIX H. MODEL RESULTS

The results detailed in this appendix includes results tables and graphs for both scenarios (i.e., status quo and alternative) by staging of the initial case of CDI (i.e., non-severe, severe, fulminant), as well as overall (i.e., all stages). The results of the model output consists of the cost effectiveness rankings in table and graph formats, the tornado diagram and table results for the Net Monetary Benefit (NMB) analysis, and the table results from the sensitivity analyses for the most influential variables in the model—efficacy of fidaxomicin and vancomycin, cost of fidaxomicin and vancomycin, and probability of death from CDI/rCDI. For non-severe CDI, efficacy of metronidazole is included in the sensitivity analysis. For the analysis of all CDI stages, the results of the tornado diagram and table results for the cost and effectiveness (in addition to NMB) are also included.

A. Non-severe CDI

1. Status Quo Scenario

Table 24. Cost Effectiveness Rankings: Status Quo Scenario--Initial, non-severe CDI

Strategy	Cost	Incr Cost	Eff	Incr Eff	Incr C/E	NMB	C/E	Dominance
Metronidizole	$159.22	0	0.7709	0	0	-159.22	206.54	
Vancomycin	$674.16	514.94	0.7287	-0.0422	-12209.3604	-674.16	925.16	(Dominated)
Fidaxomicin	$3,964.32	3805.10	0.7945	0.0236	161108.6670	-3964.32	4989.78	

Figure 17. Cost Effectiveness Analysis with WTP $100,000. Status Quo Scenario--Initial, non-severe CDI

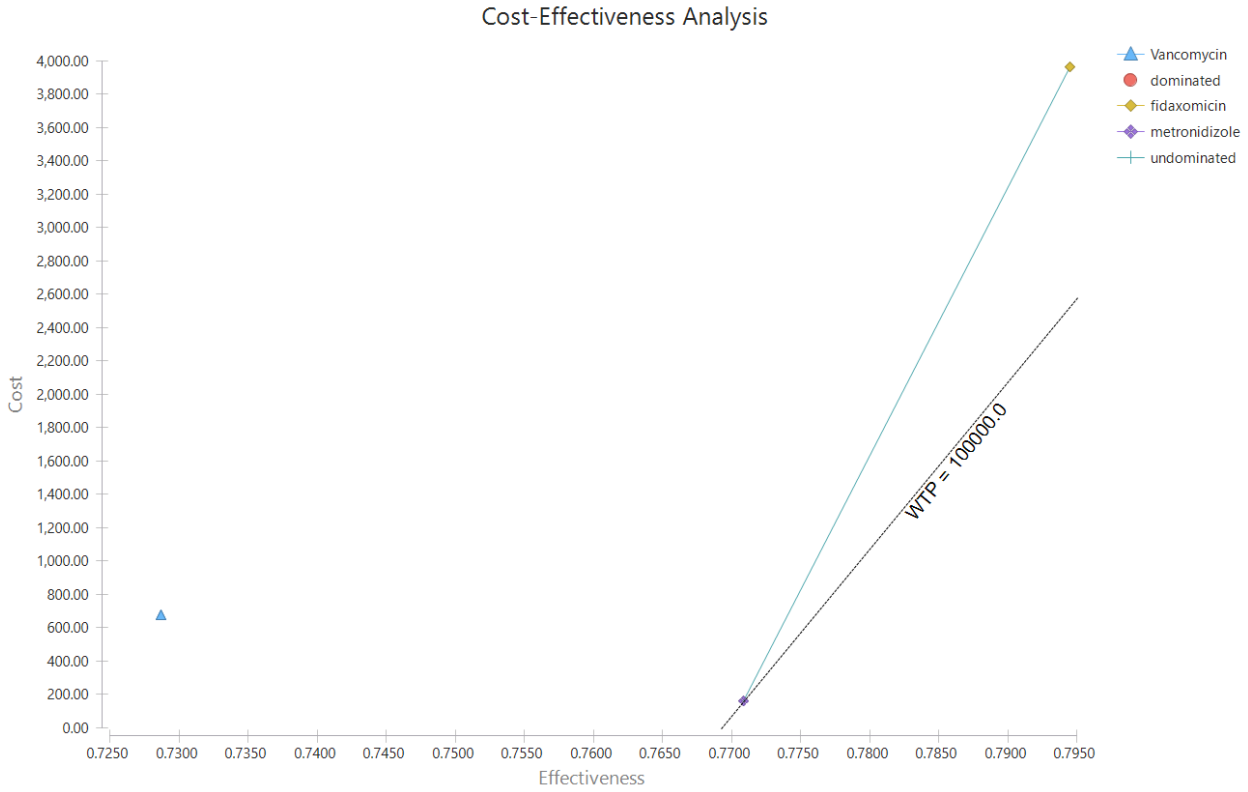


Figure 18. Tornado Diagram NMB

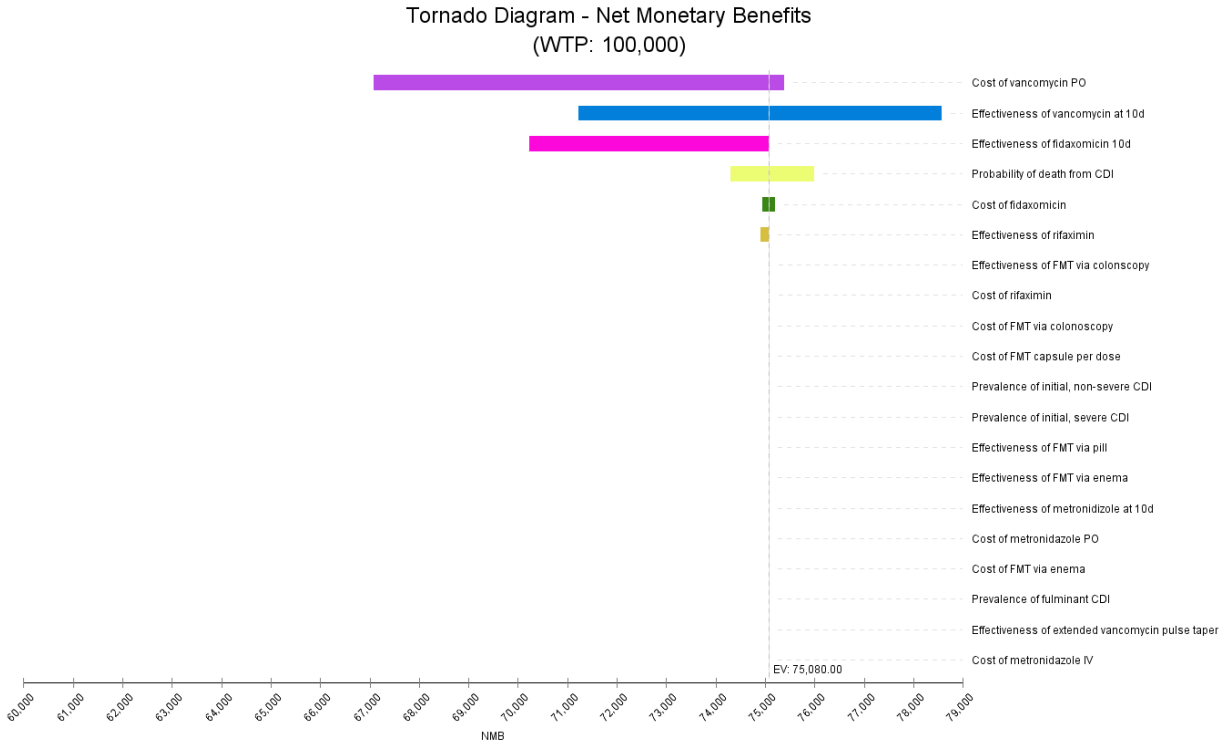


Table 25. Tornado Diagram NMB Report. Status Quo Scenario--Initial, non-severe CDI

Variable Name	Variable Low	Variable Base	Variable High	Impact	Low	High	Spread	Spread²	Risk %	Cum Risk %
eff_metronidizole	0	0.75	0.75	Increase	75541.04	77476.79	1935.752	3747137	0.284791	0.284791
eff_vanc	0.31	0.585	0.85	Increase	76796.16	78714.31	1918.147	3679286	0.279634	0.564425
p_Death	0.0774	0.086	0.0946	Decrease	76634.97	78465.63	1830.664	3351332	0.254709	0.819133
c_vancPO	9.7	313.7	8227.7	Decrease	76208.97	77525.49	1316.524	1733234	0.13173	0.950863
eff_fidaxomicin	0	0.88	0.88	Increase	76799.19	77476.79	677.5956	459135.8	0.034895	0.985758
c_metroPO	25	64.6	454	Decrease	77087.39	77516.39	429	184041	0.013988	0.999746
eff_FMTcolonoscopy	0.8	0.87	1	Increase	77452.14	77493.22	41.08	1687.566	0.000128	0.999874
c_fidaxomicin	3550.23	3944.7	4339.17	Decrease	77456.48	77497.11	40.63041	1650.83	0.000125	1
c_FMTcolonoscopy	4814.1	5349	5883.9	Decrease	77475.56	77478.02	2.46054	6.054257	4.6E-07	1
c_FMTpill	2050	2050	6150	Increase	77476.79	77476.79	0	0	0	1
p_Initial_NS	0.459	0.51	0.561	Increase	77476.79	77476.79	0	0	0	1
p_Initial_severe	0.423	0.47	0.517	Increase	77476.79	77476.79	0	0	0	1
eff_FMTpill	0.68	0.733	0.91	Increase	77476.79	77476.79	0	0	0	1
eff_FMTenema	0	0.621	0.621	Increase	77476.79	77476.79	0	0	0	1
c_FMTenema	100	1600	3500	Increase	77476.79	77476.79	0	0	0	1
c_rifaximin	1940.4	2156	2371.6	Increase	77476.79	77476.79	0	0	0	1
p_fulminant	0.018	0.02	0.022	Increase	77476.79	77476.79	0	0	0	1
eff_rifaximin	0	0.85	0.85	Increase	77476.79	77476.79	0	0	0	1
eff_vancpulsetaper	0.549	0.61	0.671	Increase	77476.79	77476.79	0	0	0	1
c_metroIV	43.74	48.6	53.46	Increase	77476.79	77476.79	0	0	0	1

*Note: Gray cells denote variables that do not contribute to the model results.

Table 26. 1-way Sensitivity Analysis, varying Effectiveness of Metronidazole

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
0.0%	METRO	1	1616.59	0.00	0.6858	0.0000	0.00	-1616.59	2357.37	
0.0%	VANC	0	1642.02	25.43	0.7696	0.0839	303.14	-1642.02	2133.49	
0.0%	FIDA	2	4001.36	2359.34	0.7990	0.0293	80432.73	-4001.36	5008.12	
18.8%	METRO	1	1287.83	0.00	0.7083	0.0000	0.00	-1287.83	1818.26	
18.8%	VANC	0	1642.02	354.19	0.7696	0.0614	5771.89	-1642.02	2133.49	
18.8%	FIDA	2	4001.36	2359.34	0.7990	0.0293	80432.73	-4001.36	5008.12	
37.5%	METRO	1	965.14	0.00	0.7337	0.0000	0.00	-965.14	1315.48	
37.5%	VANC	0	1642.02	676.88	0.7696	0.0360	18822.42	-1642.02	2133.49	
37.5%	FIDA	2	4001.36	2359.34	0.7990	0.0293	80432.73	-4001.36	5008.12	
56.3%	METRO	1	651.30	0.00	0.7579	0.0000	0.00	-651.30	859.38	
56.3%	VANC	0	1642.02	990.72	0.7696	0.0118	84152.91	-1642.02	2133.49	
56.3%	FIDA	2	4001.36	2359.34	0.7990	0.0293	80432.73	-4001.36	5008.12	
75.0%	METRO	1	343.31	0.00	0.7823	0.0000	0.00	-343.31	438.86	
75.0%	VANC	0	1642.02	1298.70	0.7696	-0.0127	-102660.63	-1642.02	2133.49	(Dominated)
75.0%	FIDA	2	4001.36	3658.04	0.7990	0.0167	219272.92	-4001.36	5008.12	

Table 27. 1-way Sensitivity Analysis, varying Effectiveness of Vancomycin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
31.0%	METRO	1	534.54	0.00	0.7720	0.0000	0.00	-534.54	692.45	
31.0%	VANC	0	2754.20	2219.66	0.7370	-0.0350	-63443.15	-2754.20	3737.17	(Dominated)
31.0%	FIDA	2	4037.49	3502.94	0.7902	0.0183	191764.79	-4037.49	5109.27	
44.5%	METRO	1	440.35	0.00	0.7740	0.0000	0.00	-440.35	568.90	
44.5%	VANC	0	2190.73	1750.38	0.7515	-0.0225	-77790.97	-2190.73	2914.98	(Dominated)
44.5%	FIDA	2	4020.53	3580.17	0.7903	0.0163	219957.51	-4020.53	5087.21	
58.0%	METRO	1	333.51	0.00	0.7764	0.0000	0.00	-333.51	429.54	
58.0%	VANC	0	1664.38	1330.87	0.7640	-0.0124	-107020.05	-1664.38	2178.50	(Dominated)
58.0%	FIDA	2	3998.94	3665.43	0.7909	0.0145	252887.53	-3998.94	5055.98	
71.5%	METRO	1	249.52	0.00	0.7786	0.0000	0.00	-249.52	320.47	
71.5%	VANC	0	1120.40	870.88	0.7769	-0.0017	-510808.10	-1120.40	1442.12	(Dominated)
71.5%	FIDA	2	3984.21	3734.69	0.7913	0.0127	293488.10	-3984.21	5034.74	
85.0%	METRO	1	157.95	0.00	0.7809	0.0000	0.00	-157.95	202.26	
85.0%	VANC	0	565.30	407.34	0.7894	0.0085	47941.33	-565.30	716.08	
85.0%	FIDA	2	3962.62	3397.33	0.7917	0.0023	1492249.32	-3962.62	5005.17	

Table 28. 1-way Sensitivity Analysis, varying Probability of Death from CDI

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
7.7%	METRO	1	372.29	0.00	0.7848	0.00	0.00	-372.286	474.37	
7.7%	VANC	0	1710.40	1338.11	0.7752	-0.01	-139039.79	-1710.399	2206.44	(Dominated)
7.7%	FIDA	2	4021.89	3649.60	0.8027	0.02	204215.48	-4021.888	5010.58	
8.2%	METRO	1	359.90	0.00	0.7804	0.00	0.00	-359.899	461.16	
8.2%	VANC	0	1685.41	1325.51	0.7698	-0.01	-125078.72	-1685.407	2189.35	(Dominated)
8.2%	FIDA	2	4012.15	3652.25	0.7985	0.02	201549.04	-4012.149	5024.37	
8.6%	METRO	1	347.89	0.00	0.7758	0.00	0.00	-347.891	448.44	
8.6%	VANC	0	1658.69	1310.80	0.7645	-0.01	-115824.56	-1658.690	2169.76	(Dominated)

8.6%	FIDA	2	4003.32	3655.43	0.7944	0.02	196349.70	-4003.324	5039.48	
9.0%	METRO	1	331.96	0.00	0.7705	0.00	0.00	-331.957	430.85	
9.0%	VANC	0	1632.81	1300.85	0.7591	-0.01	-114064.93	-1632.806	2151.08	(Dominated)
9.0%	FIDA	2	3991.22	3659.26	0.7898	0.02	188976.41	-3991.221	5053.25	
9.5%	METRO	1	322.09	0.00	0.7671	0.00	0.00	-322.092	419.88	
9.5%	VANC	0	1613.89	1291.80	0.7556	-0.01	-112619.45	-1613.890	2135.83	(Dominated)
9.5%	FIDA	2	3984.40	3662.31	0.7870	0.02	184399.82	-3984.397	5063.03	

Table 29. 1-way Sensitivity Analysis, varying Cost of Vancomycin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
$9.70	METRO	1	295.28	0.00	0.7837	0.0000	0.00	-295.28	376.76	
$9.70	VANC	0	1349.87	1054.59	0.7718	-0.0120	-87976.03	-1349.87	1749.10	(Dominated)
$9.70	FIDA	2	3992.46	3697.17	0.7997	0.0160	231243.20	-3992.46	4992.27	
$2,064	METRO	1	639.00	0.00	0.7837	0.0000	0.00	-639.00	815.32	
$2,064	VANC	0	3426.77	2787.77	0.7718	-0.0120	-232561.12	-3426.77	4440.24	(Dominated)
$2,064	FIDA	2	4064.16	3425.16	0.7997	0.0160	214229.71	-4064.16	5081.92	
$4,119	METRO	1	982.72	0.00	0.7837	0.0000	0.00	-982.72	1253.88	
$4,119	FIDA	2	4135.86	3153.14	0.7997	0.0160	197216.22	-4135.86	5171.58	
$4,119	VANC	0	5503.66	1367.80	0.7718	-0.0280	-48892.89	-5503.66	7131.38	(Dominated)
$6,173	METRO	1	1326.44	0.00	0.7837	0.0000	0.00	-1326.44	1692.45	
$6,173	FIDA	2	4207.56	2881.12	0.7997	0.0160	180202.72	-4207.56	5261.24	
$6,173	VANC	0	7580.56	3372.99	0.7718	-0.0280	-120569.66	-7580.56	9822.52	(Dominated)
$8,228	METRO	1	1670.16	0.00	0.7837	0.0000	0.00	-1670.16	2131.01	
$8,228	FIDA	2	4279.26	2609.11	0.7997	0.0160	163189.23	-4279.26	5350.90	
$8,228	VANC	0	9657.45	5378.19	0.7718	-0.0280	-192246.43	-9657.45	12513.66	(Dominated)

Table 30. 1-way Sensitivity Analysis, varying Effectiveness of Fidaxomicin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
0.0%	METRO	1	586.48	0.00	0.7771	0.0000	0.00	-586.48	754.70	
0.0%	VANC	0	2502.48	1916.00	0.7263	-0.0508	-37718.37	-2502.48	3445.49	(Dominated)
0.0%	FIDA	2	6899.33	6312.85	0.6529	-0.1242	-50826.42	-6899.33	10567.21	(Dominated)
22.0%	METRO	1	522.83	0.00	0.7780	0.0000	0.00	-522.83	672.05	
22.0%	VANC	0	2290.38	1767.55	0.7388	-0.0392	-45082.45	-2290.38	3100.31	(Dominated)
22.0%	FIDA	2	5931.17	5408.34	0.6921	-0.0859	-62949.63	-5931.17	8570.43	(Dominated)
44.0%	METRO	1	463.46	0.00	0.7791	0.0000	0.00	-463.46	594.82	
44.0%	VANC	0	2072.98	1609.52	0.7488	-0.0304	-52997.39	-2072.98	2768.48	(Dominated)
44.0%	FIDA	2	5114.92	4651.47	0.7314	-0.0477	-97463.53	-5114.92	6993.11	(Dominated)
66.0%	METRO	1	407.29	0.00	0.7806	0.0000	0.00	-407.29	521.79	
66.0%	VANC	0	1880.35	1473.06	0.7584	-0.0222	-66350.70	-1880.35	2479.47	(Dominated)
66.0%	FIDA	2	4482.76	4075.47	0.7682	-0.0124	-329619.87	-4482.76	5835.36	(Dominated)
88.0%	METRO	1	338.29	0.00	0.7821	0.0000	0.00	-338.29	432.54	
88.0%	VANC	0	1668.54	1330.26	0.7696	-0.0125	-106799.16	-1668.54	2167.94	(Dominated)

88.0%	FIDA	2	3998.36	3660.07	0.7988	0.0167	219093.46	-3998.36	5005.41	

2. Alternative Scenario

Table 31. Alterative Scenario. Cost Effectiveness Rankings: Initial, non-severe CDI

Strategy	Cost	Incr Cost	Eff	Incr Eff	Incr C/E	NMB	C/E	Dominated
Metronidizole	$159.22		0.7709			-159.22	206.54	
Vancomycin	$623.82	464.60	0.7250	-0.0458	-10133.95	-623.82	860.42	(Dominated)
FMT	$2,165.84	2006.62	0.7568	-0.0141	-142661.18	-2165.84	2861.83	(Dominated)
Fidaxomicin	$3,964.32	3805.10	0.7945	0.0236	161108.67	-3964.32	4989.78	

Figure 19. Cost Effectiveness Analysis with WTP $100,000

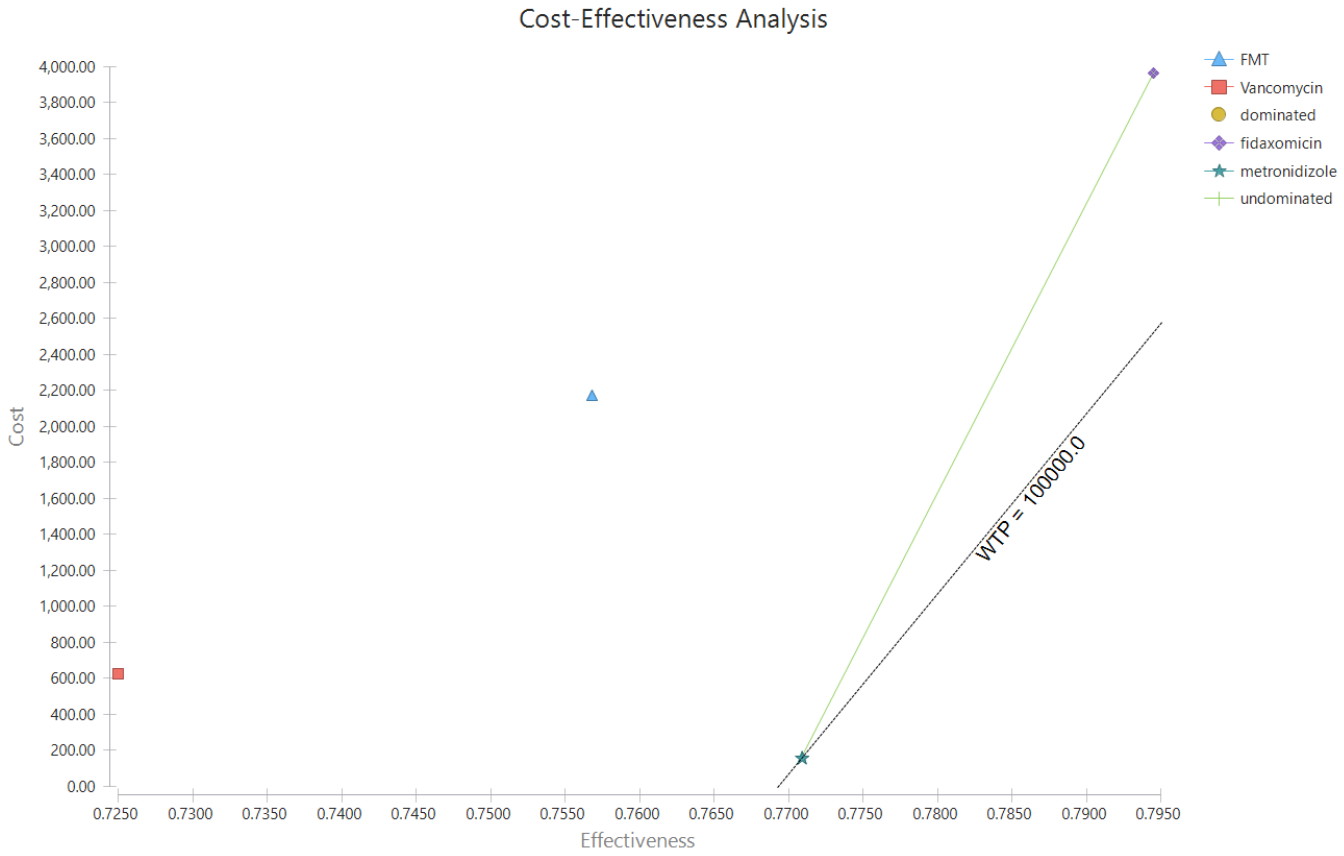


Figure 20. Tornado Diagram NMB

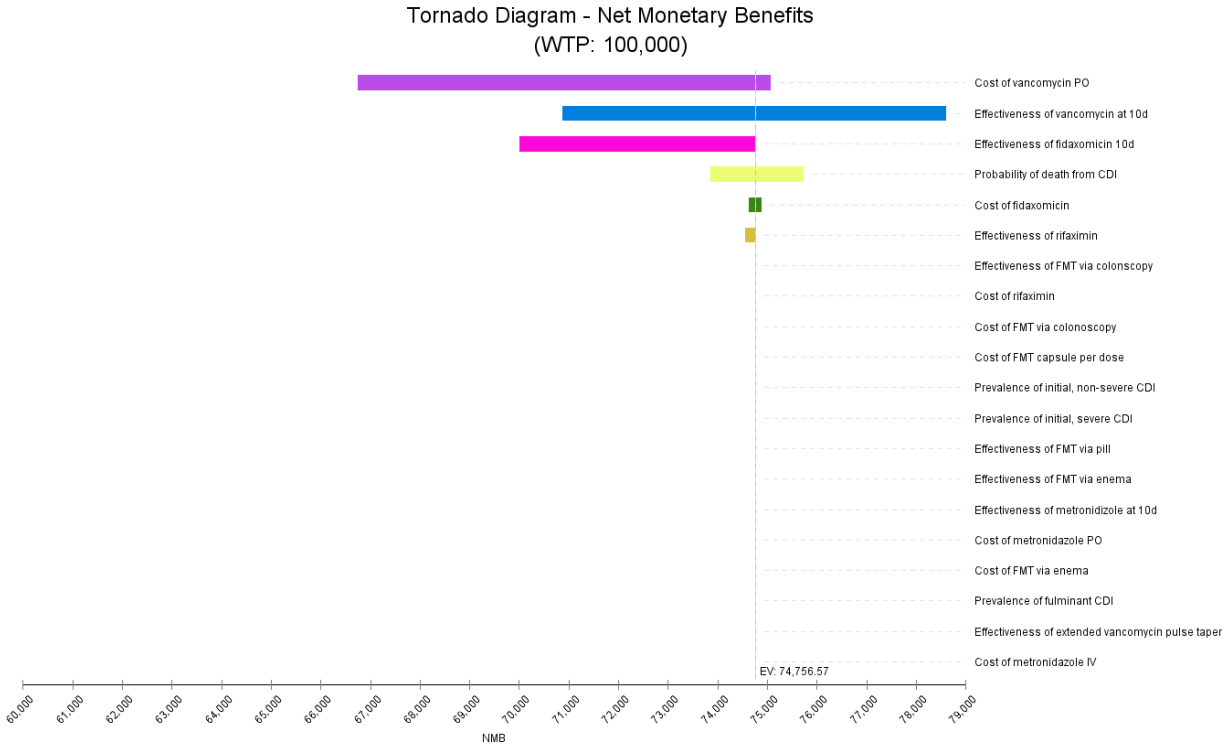


Table 32. Tornado Diagram NMB Report

Variable Name	Variable Low	Variable Base	Variable High	Impact	Low	High	Spread	Spread²	Risk %	Cum Risk %
c_vancPO	9.7	313.7	8227.7	Decrease	66748.39	75064.19	8315.794	69152433	0.445267	0.445267
eff_vanc	0.31	0.585	0.85	Increase	70867.72	78605.73	7738.011	59876812	0.385542	0.830809
eff_fidaxomicin	0	0.88	0.88	Increase	70004.21	74756.57	4752.363	22584953	0.145423	0.976231
p_Death	0.0774	0.086	0.0946	Decrease	73849.21	75742.13	1892.914	3583124	0.023071	0.999303
c_fidaxomicin	3550.23	3944.7	4339.17	Decrease	74624.62	74888.52	263.9004	69643.44	0.000448	0.999751
eff_rifaximin	0	0.85	0.85	Increase	74560.28	74756.57	196.2939	38531.3	0.000248	0.999999
eff_FMTcolonoscopy	0.8	0.87	0.9999	Increase	74756.57	74764.41	7.84	61.4656	3.96E-07	1
c_rifaximin	1940.4	2156	2371.6	Decrease	74754.01	74759.14	5.13128	26.33003	1.7E-07	1
c_FMTcolonoscopy	4814.1	5349	5883.9	Decrease	74756.36	74756.78	0.42792	0.183116	1.18E-09	1
c_FMTpill	2050	2050	6150	Increase	74756.57	74756.57	0	0	0	1
p_Initial_NS	0.459	0.51	0.561	Increase	74756.57	74756.57	0	0	0	1
p_Initial_severe	0.423	0.47	0.517	Increase	74756.57	74756.57	0	0	0	1
eff_FMTpill	0.68	0.733	0.91	Increase	74756.57	74756.57	0	0	0	1
eff_FMTenema	0	0.621	0.621	Increase	74756.57	74756.57	0	0	0	1
eff_metronidizole	0	0.75	0.75	Increase	74756.57	74756.57	0	0	0	1
c_metroPO	25	64.6	454	Increase	74756.57	74756.57	0	0	0	1
c_FMTenema	100	1600	3500	Increase	74756.57	74756.57	0	0	0	1
p_fulminant	0.018	0.02	0.022	Increase	74756.57	74756.57	0	0	0	1
eff_vancpulsetaper	0.549	0.61	0.671	Increase	74756.57	74756.57	0	0	0	1
c_metroIV	43.74	48.6	53.46	Increase	74756.57	74756.57	0	0	0	1

*Note: Gray cells denote variables that do not contribute to the model results.

Table 33. 1-way Sensitivity Analysis, varying Cost of Vancomycin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Domina
$9.70	METRO	1	991.05	0.00	0.7862	0.0000	0.00	-991.05	1260.51	
$9.70	VANC	0	1333.76	342.71	0.7669	-0.0193	-17762.77	-1333.76	1739.08	(Domina
$9.70	FIDA	2	4004.05	3013.00	0.7956	0.0093	322558.47	-4004.05	5032.95	
$9.70	FMT	3	5580.08	1576.03	0.8070	0.0114	138424.86	-5580.08	6915.00	
$2,064.20	METRO	1	991.05	0.00	0.7862	0.0000	0.00	-991.05	1260.51	
$2,064.20	VANC	0	3413.94	2422.89	0.7669	-0.0193	-125579.65	-3413.94	4451.42	(Domina
$2,064.20	FIDA	2	4078.01	3086.96	0.7956	0.0093	330476.52	-4078.01	5125.92	
$2,064.20	FMT	3	5580.08	1502.07	0.8070	0.0114	131928.68	-5580.08	6915.00	
$4,118.70	METRO	1	991.05	0.00	0.7862	0.0000	0.00	-991.05	1260.51	
$4,118.70	VANC	2	4151.97	3160.92	0.7956	0.0093	338394.56	-4151.97	5218.89	
$4,118.70	FIDA	0	5494.12	1342.15	0.7669	-0.0286	-46871.56	-5494.12	7163.76	(Domina
$4,118.70	FMT	3	5580.08	1428.11	0.8070	0.0114	125432.50	-5580.08	6915.00	
$6,173.20	METRO	1	991.05	0.00	0.7862	0.0000	0.00	-991.05	1260.51	
$6,173.20	FIDA	2	4225.93	3234.89	0.7956	0.0093	346312.61	-4225.93	5311.85	
$6,173.20	FMT	3	5580.08	1354.14	0.8070	0.0114	118936.32	-5580.08	6915.00	
$6,173.20	VANC	0	7574.30	1994.22	0.7669	-0.0400	-49830.58	-7574.30	9876.10	(Domina
$8,227.70	METRO	1	991.05	0.00	0.7862	0.0000	0.00	-991.05	1260.51	
$8,227.70	FIDA	2	4299.89	3308.85	0.7956	0.0093	354230.66	-4299.89	5404.82	
$8,227.70	FMT	3	5580.08	1280.18	0.8070	0.0114	112440.14	-5580.08	6915.00	
$8,227.70	VANC	0	9654.48	4074.40	0.7669	-0.0400	-101809.06	-9654.48	12588.45	(Domina

Table 34. 1-way Sensitivity Analysis, varying Effectiveness of Vancomycin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
31.0%	METRO	1	965.37	0.00	0.7847	0.0000	0.00	-965.37	1230.21	
31.0%	VANC	0	2756.23	1790.86	0.7397	-0.0450	-39811.82	-2756.23	3725.96	(Dominated)
31.0%	FIDA	2	4027.73	3062.35	0.7940	0.0093	328621.79	-4027.73	5072.46	
31.0%	FMT	3	5565.63	1537.91	0.8057	0.0116	132414.65	-5565.63	6908.24	
44.5%	METRO	1	965.37	0.00	0.7847	0.0000	0.00	-965.37	1230.21	
44.5%	VANC	0	2222.95	1257.58	0.7528	-0.0319	-39387.89	-2222.95	2952.94	(Dominated)
44.5%	FIDA	2	4011.55	3046.18	0.7947	0.0100	304958.12	-4011.55	5047.83	
44.5%	FMT	3	5565.63	1554.08	0.8057	0.0109	141999.61	-5565.63	6908.24	
58.0%	METRO	1	965.37	0.00	0.7847	0.0000	0.00	-965.37	1230.21	
58.0%	VANC	0	1670.74	705.37	0.7661	-0.0186	-37929.22	-1670.74	2180.78	(Dominated)
58.0%	FIDA	2	3992.48	3027.11	0.7951	0.0104	290419.46	-3992.48	5021.09	
58.0%	FMT	3	5565.63	1573.16	0.8057	0.0105	149683.35	-5565.63	6908.24	
71.5%	METRO	1	965.37	0.00	0.7847	0.0000	0.00	-965.37	1230.21	
71.5%	VANC	0	1102.75	137.38	0.7796	-0.0051	-26723.29	-1102.75	1414.54	(Dominated)
71.5%	FIDA	2	3978.67	3013.30	0.7955	0.0108	278213.72	-3978.67	5001.16	
71.5%	FMT	3	5565.63	1586.96	0.8057	0.0101	157090.26	-5565.63	6908.24	
85.0%	VANC	0	567.17	0.00	0.7922	0.0000	0.00	-567.17	715.94	
85.0%	METRO	1	965.37	398.20	0.7847	-0.0075	-53216.76	-965.37	1230.21	(Dominated)
85.0%	FIDA	2	3964.19	3397.02	0.7960	0.0038	904475.78	-3964.19	4980.40	
85.0%	FMT	3	5565.63	1601.45	0.8057	0.0097	165188.39	-5565.63	6908.24	

Table 35. 1-way Sensitivity Analysis, varying Effectiveness of Fidaxomicin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
0.0%	METRO	1	983.56	0.00	0.7870	0.0000	0.00	-983.56	1249.69	
0.0%	VANC	0	2462.34	1478.78	0.7294	-0.0576	-25659.53	-2462.34	3375.79	(Dominated)
0.0%	FMT	3	5567.24	4583.68	0.8084	0.0214	214541.49	-5567.24	6886.67	
0.0%	FIDA	2	6879.45	1312.21	0.6539	-0.1545	-8495.58	-6879.45	10519.85	(Dominated)
22.0%	METRO	1	983.56	0.00	0.7870	0.0000	0.00	-983.56	1249.69	
22.0%	VANC	0	2245.84	1262.28	0.7401	-0.0470	-26882.51	-2245.84	3034.56	(Dominated)
22.0%	FMT	3	5567.24	4583.68	0.8084	0.0214	214541.49	-5567.24	6886.67	
22.0%	FIDA	2	5869.91	302.67	0.6958	-0.1126	-2687.80	-5869.91	8436.23	(Dominated)
44.0%	METRO	1	983.56	0.00	0.7870	0.0000	0.00	-983.56	1249.69	
44.0%	VANC	0	2046.09	1062.53	0.7500	-0.0370	-28698.89	-2046.09	2728.05	(Dominated)
44.0%	FIDA	2	5080.73	4097.17	0.7347	-0.0524	-78218.41	-5080.73	6915.74	(Dominated)
44.0%	FMT	3	5567.24	4583.68	0.8084	0.0214	214541.49	-5567.24	6886.67	
66.0%	METRO	1	983.56	0.00	0.7870	0.0000	0.00	-983.56	1249.69	
66.0%	VANC	0	1839.43	855.87	0.7600	-0.0270	-31701.01	-1839.43	2420.15	(Dominated)
66.0%	FIDA	2	4456.87	3473.31	0.7686	-0.0184	-188823.77	-4456.87	5798.32	(Dominated)
66.0%	FMT	3	5567.24	4583.68	0.8084	0.0214	214541.49	-5567.24	6886.67	
88.0%	METRO	1	983.56	0.00	0.7870	0.0000	0.00	-983.56	1249.69	
88.0%	VANC	0	1646.80	663.24	0.7692	-0.0179	-37081.76	-1646.80	2141.04	(Dominated)
88.0%	FIDA	2	4002.38	3018.82	0.7969	0.0099	305104.02	-4002.38	5022.21	
88.0%	FMT	3	5567.24	1564.86	0.8084	0.0115	136423.27	-5567.24	6886.67	

Table 36. 1-way Sensitivity Analysis, varying Probability of death from CDI

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
7.7%	METRO	1	1025.28	0.00	0.7931	0.0000	0.00	-1025.28	1292.79	
7.7%	VANC	0	1650.65	625.37	0.7760	-0.0171	-36568.28	-1650.65	2127.18	(Dominated)
7.7%	FIDA	2	4019.66	2994.38	0.8029	0.0098	303998.93	-4019.66	5006.25	
7.7%	FMT	3	5624.47	1604.81	0.8136	0.0107	150419.84	-5624.47	6913.10	
8.2%	METRO	1	1000.68	0.00	0.7897	0.0000	0.00	-1000.68	1267.14	
8.2%	VANC	0	1631.42	630.74	0.7721	-0.0177	-35722.66	-1631.42	2113.08	(Dominated)
8.2%	FIDA	2	4010.97	3010.30	0.7999	0.0102	295697.85	-4010.97	5014.38	
8.2%	FMT	3	5602.01	1591.03	0.8104	0.0105	152007.68	-5602.01	6912.97	
8.6%	METRO	1	974.46	0.00	0.7861	0.0000	0.00	-974.46	1239.63	
8.6%	VANC	0	1612.53	638.07	0.7681	-0.0180	-35515.78	-1612.53	2099.31	(Dominated)
8.6%	FIDA	2	4004.88	3030.41	0.7968	0.0107	284022.43	-4004.88	5026.44	
8.6%	FMT	3	5580.61	1575.74	0.8071	0.0104	152073.21	-5580.61	6914.20	
9.0%	METRO	1	952.53	0.00	0.7832	0.0000	0.00	-952.53	1216.14	
9.0%	VANC	0	1593.61	641.07	0.7646	-0.0186	-34444.00	-1593.61	2084.14	(Dominated)
9.0%	FIDA	2	3996.68	3044.15	0.7944	0.0112	272836.23	-3996.68	5031.05	
9.0%	FMT	3	5564.03	1567.35	0.8046	0.0102	153934.37	-5564.03	6915.40	
9.5%	METRO	1	928.46	0.00	0.7797	0.0000	0.00	-928.46	1190.78	
9.5%	VANC	0	1575.80	647.34	0.7608	-0.0189	-34197.74	-1575.80	2071.29	(Dominated)
9.5%	FIDA	2	3990.39	3061.93	0.7914	0.0116	262852.56	-3990.39	5042.45	
9.5%	FMT	3	5542.10	1551.71	0.8013	0.0100	155335.50	-5542.10	6915.96	

Table 37. 1-way Sensitivity Analysis, varying Cost of Fidaxomicin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
$3,550	METRO	1	1007.09	0.00	0.7859	0.0000	0.00	-1007.09	1281.41	
$3,550	VANC	0	1513.28	506.19	0.7671	-0.0188	-26920.64	-1513.28	1972.67	(Dominated)
$3,550	FIDA	2	3608.40	2601.30	0.7960	0.0101	257559.90	-3608.40	4533.01	
$3,550	FMT	3	5587.03	1978.63	0.8071	0.0111	178522.22	-5587.03	6922.27	
$3,747	METRO	1	1007.09	0.00	0.7859	0.0000	0.00	-1007.09	1281.41	
$3,747	VANC	0	1578.29	571.20	0.7671	-0.0188	-30377.98	-1578.29	2057.42	(Dominated)
$3,747	FIDA	2	3808.12	2801.02	0.7960	0.0101	277334.57	-3808.12	4783.91	
$3,747	FMT	3	5587.03	1778.91	0.8071	0.0111	160502.47	-5587.03	6922.27	
$3,945	METRO	1	1007.09	0.00	0.7859	0.0000	0.00	-1007.09	1281.41	
$3,945	VANC	0	1643.30	636.21	0.7671	-0.0188	-33835.32	-1643.30	2142.16	(Dominated)
$3,945	FIDA	2	4007.84	3000.74	0.7960	0.0101	297109.23	-4007.84	5034.81	
$3,945	FMT	3	5587.03	1579.19	0.8071	0.0111	142482.71	-5587.03	6922.27	
$4,142	METRO	1	1007.09	0.00	0.7859	0.0000	0.00	-1007.09	1281.41	
$4,142	VANC	0	1708.31	701.22	0.7671	-0.0188	-37292.66	-1708.31	2226.91	(Dominated)
$4,142	FIDA	2	4207.56	3200.46	0.7960	0.0101	316883.90	-4207.56	5285.70	
$4,142	FMT	3	5587.03	1379.47	0.8071	0.0111	124462.95	-5587.03	6922.27	
$4,339	METRO	1	1007.09	0.00	0.7859	0.0000	0.00	-1007.09	1281.41	
$4,339	VANC	0	1773.32	766.23	0.7671	-0.0188	-40749.99	-1773.32	2311.65	(Dominated)
$4,339	FIDA	2	4407.28	3400.18	0.7960	0.0101	336658.56	-4407.28	5536.60	
$4,339	FMT	3	5587.03	1179.75	0.8071	0.0111	106443.20	-5587.03	6922.27	

B. Severe CDI

1. Status Quo Scenario

Table 38. Status Quo Scenario. Cost Effectiveness Rankings: Initial, severe CDI

Strategy	Cost	Incr Cost	Eff	Incr Eff	Incr C/E	NMB	C/E	Dominance
Vancomycin	$674.16		0.6477			-674.16	1040.88	
Fidaxomicin	$3,964.32	3290.16	0.7062	0.0586	56186.3234	-3964.32	5613.29	

Figure 21. Cost Effectiveness Analysis with WTP $100,000

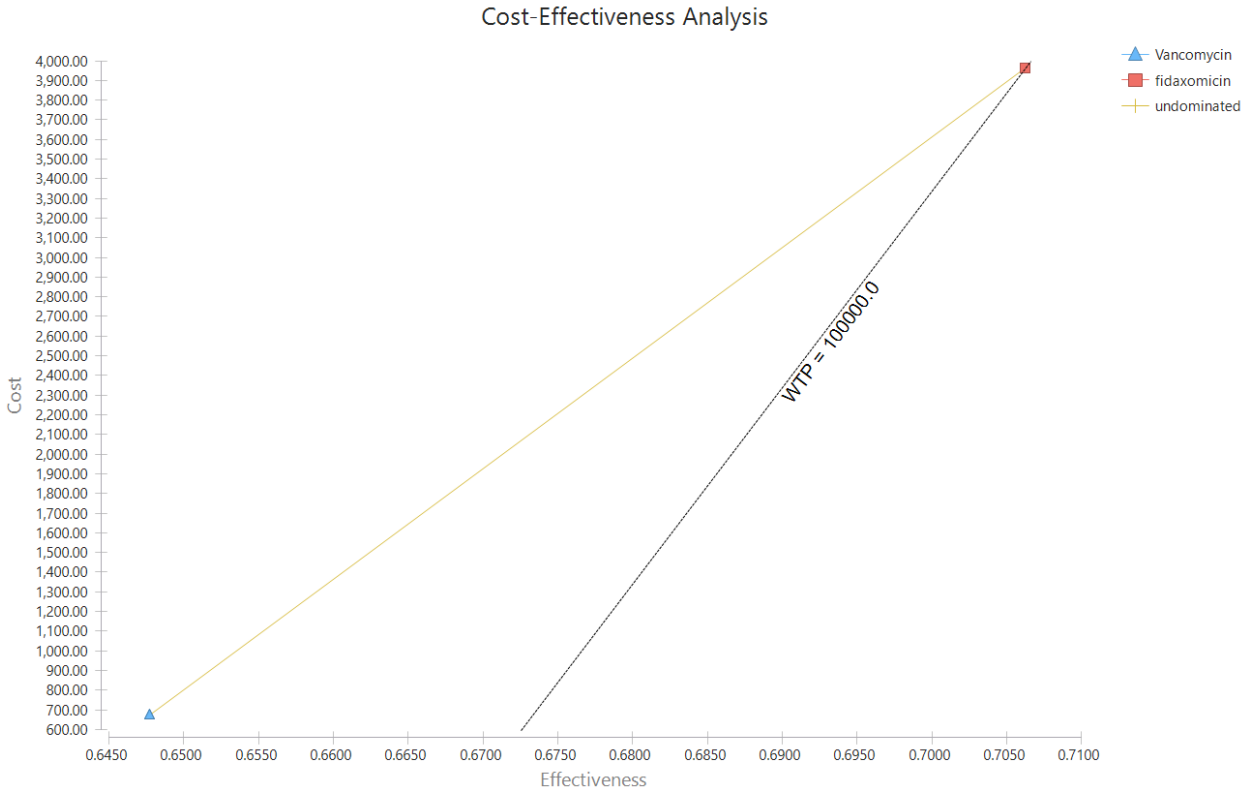


Figure 22. Tornado Diagram NMB

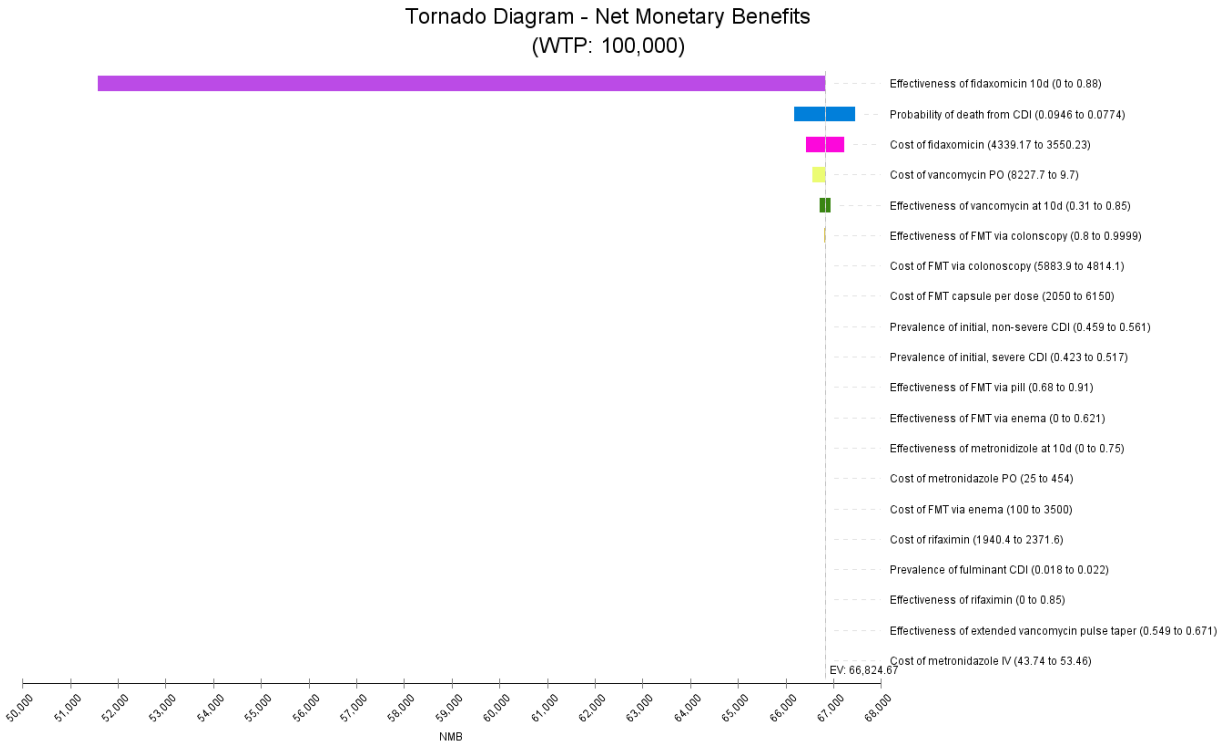


Table 39. Tornado Diagram NMB Report

Variable Name	Variable Low	Variable Base	Variable High	Impact	Low	High	Spread	Spread²	Risk %	Cum Risk %
eff_fidaxomicin	0	0.88	0.88	Increase	50999.43	66534.3	15534.88	2.41E+08	0.992139	0.992139
p_Death	0.0774	0.086	0.0946	Decrease	66024.68	67099.45	1074.764	1155117	0.004749	0.996887
c_fidaxomicin	3550.23	3944.7	4339.17	Decrease	66135.81	66932.8	796.9872	635188.6	0.002611	0.999499
c_vancPO	9.7	313.7	8227.7	Decrease	66285.01	66543.88	258.867	67012.12	0.000275	0.999774
eff_vanc	0.31	0.585	0.85	Increase	66415.66	66650.07	234.4086	54947.39	0.000226	1
c_FMTcolonoscopy	4814.1	5349	5883.9	Decrease	66534.2	66534.41	0.21396	0.045779	1.88E-10	1
c_FMTpill	2050	2050	6150	Increase	66534.3	66534.3	0	0	0	1
eff_FMTcolonoscopy	0.8	0.87	0.9999	Increase	66534.3	66534.3	0	0	0	1
p_Initial_NS	0.459	0.51	0.561	Increase	66534.3	66534.3	0	0	0	1
p_Initial_severe	0.423	0.47	0.517	Increase	66534.3	66534.3	0	0	0	1
eff_FMTpill	0.68	0.733	0.91	Increase	66534.3	66534.3	0	0	0	1
eff_FMTenema	0	0.621	0.621	Increase	66534.3	66534.3	0	0	0	1
eff_metronidizole	0	0.75	0.75	Increase	66534.3	66534.3	0	0	0	1
c_metroPO	25	64.6	454	Increase	66534.3	66534.3	0	0	0	1
c_FMTenema	100	1600	3500	Increase	66534.3	66534.3	0	0	0	1
c_rifaximin	1940.4	2156	2371.6	Increase	66534.3	66534.3	0	0	0	1
p_fulminant	0.018	0.02	0.022	Increase	66534.3	66534.3	0	0	0	1
eff_rifaximin	0	0.85	0.85	Increase	66534.3	66534.3	0	0	0	1
eff_vancpulsetaper	0.549	0.61	0.671	Increase	66534.3	66534.3	0	0	0	1
c_metroIV	43.74	48.6	53.46	Increase	66534.3	66534.3	0	0	0	1

*Note: Gray cells denote variables that do not contribute to the model results.

Table 40. 1-way Sensitivity Analysis, varying Effectiveness of Fidaxomicin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
0.0%	VANC	1	2448.1	0.00	0.6504	0.0000	0.00	-2448.15	3764.24	
0.0%	FIDA	0	6842.1	4393.92	0.5850	-0.0653	-67238.26	-6842.07	11695.39	(Dominated)
22.0%	VANC	1	2239.3	0.00	0.6584	0.0000	0.00	-2239.26	3400.94	
22.0%	FIDA	0	5853.0	3613.74	0.6196	-0.0388	-93064.91	-5853.01	9446.52	(Dominated)
44.0%	VANC	1	2040.9	0.00	0.6658	0.0000	0.00	-2040.91	3065.37	
44.0%	FIDA	0	5075.1	3034.19	0.6528	-0.0130	-232606.09	-5075.11	7774.92	(Dominated)
66.0%	VANC	1	1840.9	0.00	0.6748	0.0000	0.00	-1840.88	2727.87	
66.0%	FIDA	0	4441.6	2600.73	0.6828	0.0079	328512.86	-4441.60	6505.39	
88.0%	VANC	1	1645.4	0.00	0.6831	0.0000	0.00	-1645.45	2408.72	
88.0%	FIDA	0	3990.5	2345.04	0.7111	0.0280	83709.47	-3990.49	5611.43	

Table 41. 1-way Sensitivity Analysis, varying Probability of Death from CDI

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
7.7%	VANC	1	1678.63	0.00	0.6899	0.0000	0.00	-1678.63	2432.98	
7.7%	FIDA	0	4022.43	2343.80	0.7125	0.0226	103823.59	-4022.43	5645.32	
8.2%	VANC	1	1658.48	0.00	0.6862	0.0000	0.00	-1658.48	2416.79	
8.2%	FIDA	0	4011.91	2353.44	0.7097	0.0234	100375.97	-4011.91	5653.13	
8.6%	VANC	1	1635.57	0.00	0.6820	0.0000	0.00	-1635.57	2398.17	
8.6%	FIDA	0	4001.24	2365.67	0.7065	0.0245	96467.31	-4001.24	5663.21	
9.0%	VANC	1	1612.50	0.00	0.6779	0.0000	0.00	-1612.50	2378.78	
9.0%	FIDA	0	3996.38	2383.87	0.7038	0.0259	91875.05	-3996.38	5678.14	
9.5%	VANC	1	1590.62	0.00	0.6739	0.0000	0.00	-1590.62	2360.33	
9.5%	FIDA	0	3987.63	2397.02	0.7012	0.0273	87807.38	-3987.63	5686.92	

Table 42. 1-way Sensitivity Analysis, varying Cost of Fidaxomicin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
$3,550.23	VANC	1	1506.68	0.00	0.6782	0.0000	0.00	-1506.68	2221.48	
$3,550.23	FIDA	0	3596.03	2089.35	0.7031	0.0249	83879.79	-3596.03	5114.24	
$3,747.47	VANC	1	1571.13	0.00	0.6782	0.0000	0.00	-1571.13	2316.51	
$3,747.47	FIDA	0	3795.12	2223.99	0.7031	0.0249	89284.79	-3795.12	5397.38	
$3,944.70	VANC	1	1635.59	0.00	0.6782	0.0000	0.00	-1635.59	2411.55	
$3,944.70	FIDA	0	3994.21	2358.62	0.7031	0.0249	94689.79	-3994.21	5680.52	
$4,141.94	VANC	1	1700.05	0.00	0.6782	0.0000	0.00	-1700.05	2506.59	
$4,141.94	FIDA	0	4193.30	2493.25	0.7031	0.0249	100094.79	-4193.30	5963.67	
$4,339.17	VANC	1	1764.50	0.00	0.6782	0.0000	0.00	-1764.50	2601.62	
$4,339.17	FIDA	0	4392.39	2627.88	0.7031	0.0249	105499.79	-4392.39	6246.81	

Table 43. 1-way Sensitivity Analysis, varying Cost of Vancomycin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
$9.70	VANC	1	1310.38	0.00	0.6822	0.0000	0.00	-1310.38	1920.68	
$9.70	FIDA	0	3987.65	2677.27	0.7087	0.0264	101351.95	-3987.65	5627.01	
$2,064.20	VANC	1	3388.50	0.00	0.6822	0.0000	0.00	-3388.50	4966.69	
$2,064.20	FIDA	0	4054.83	666.33	0.7087	0.0264	25224.76	-4054.83	5721.81	
$4,118.70	VANC	0	4122.01	0.00	0.7087	0.0000	0.00	-4122.01	5816.61	
$4,118.70	FIDA	1	5466.63	1344.62	0.6822	-0.0264	-50902.43	-5466.63	8012.70	(Dominated

$6,173.20	FIDA	0	4189.19	0.00	0.7087	0.0000	0.00	-4189.19	5911.42	
$6,173.20	VANC	1	7544.76	3355.56	0.6822	-0.0264	-127029.61	-7544.76	11058.70	(Dominated
$8,227.70	FIDA	0	4256.38	0.00	0.7087	0.0000	0.00	-4256.38	6006.22	
$8,227.70	VANC	1	9622.88	5366.51	0.6822	-0.0264	-203156.80	-9622.88	14104.71	(Dominated

2. Alterative Scenario

Table 44. Alterative Scenario with FMT. Cost Effectiveness Rankings: Initial, severe CDI

Strategy	Cost	Incr Cost	Eff	Incr Eff	Incr C/E	NMB	C/E	Dominance
Vancomycin	$623.82		0.6444			-623.82	968.01	
FMT	$2,165.84	1542.02	0.6727	0.0283	54468.23	-2165.84	3219.41	(Dominated)
Fidaxomicin	$3,964.32	3340.50	0.7062	0.0618	54050.89	-3964.32	5613.29	

Figure 23. Cost Effectiveness Analysis with WTP $100,000

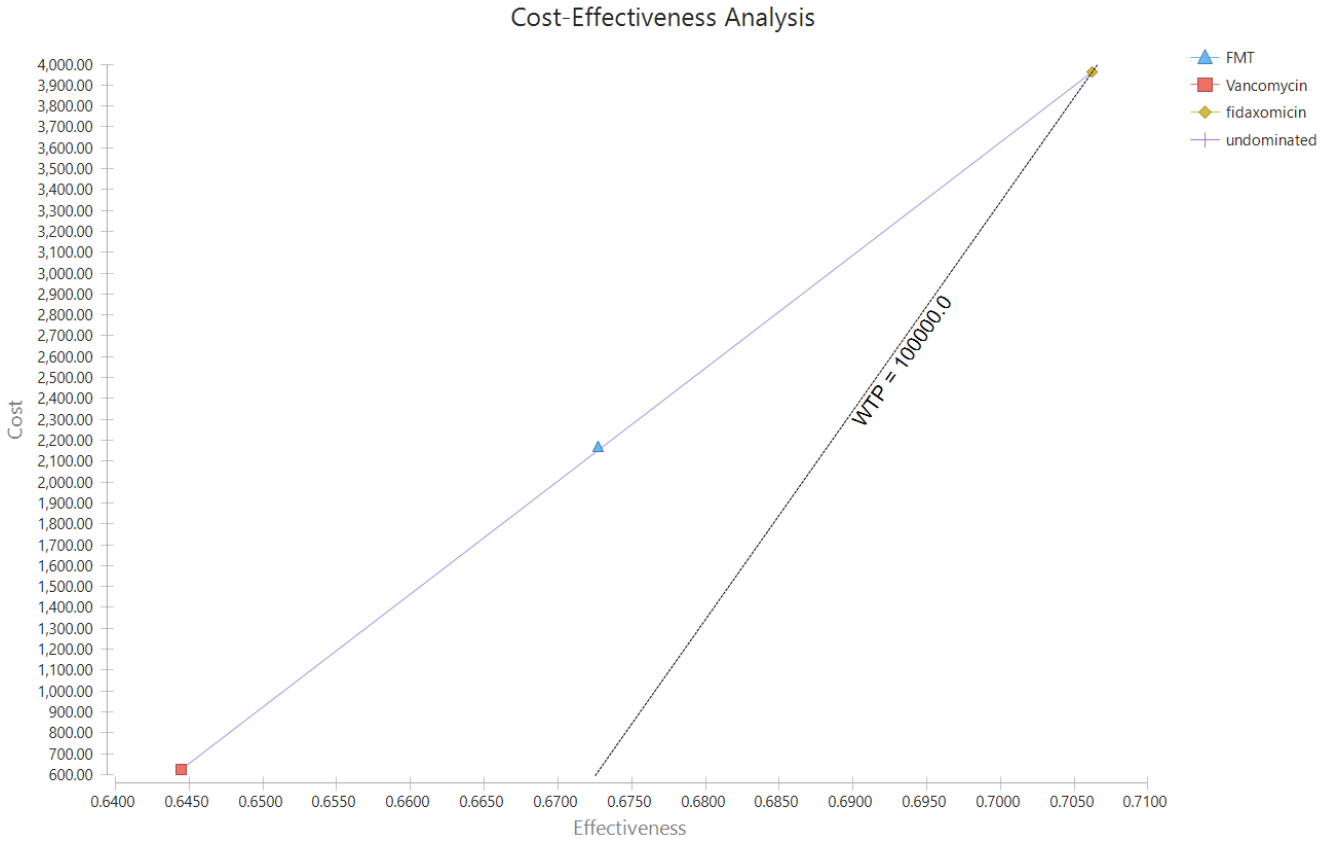


Figure 24. Tornado Diagram NMB

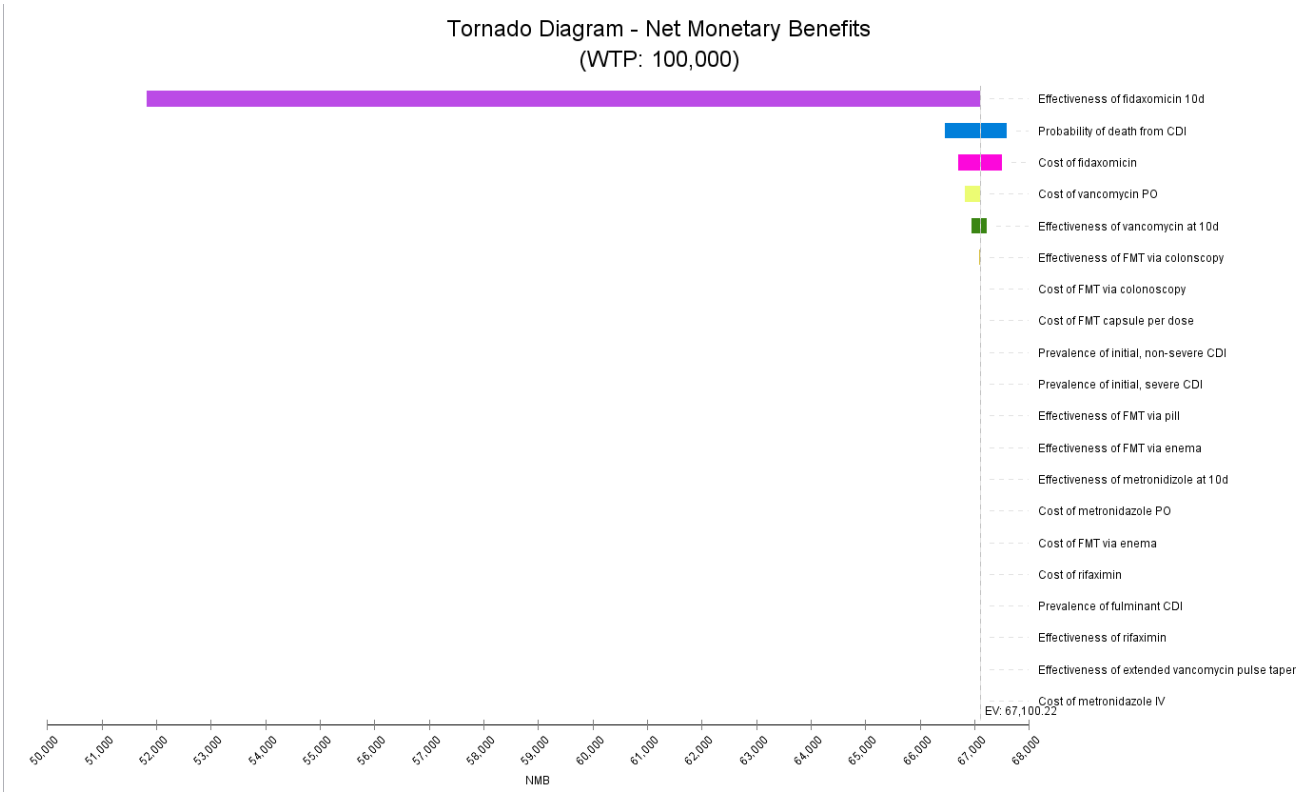


Table 45. Tornado Diagram NMB Report

Variable Name	Variable Low	Variable Base	Variable High	Impact	Low	High	Spread	Spread²	Risk %	Cum Risk %
eff_fidaxomicin	0	0.88	0.88	Increase	51827.34	67100.22	15272.88	2.33E+08	0.991213	0.991213
p_Death	0.0774	0.086	0.0946	Decrease	66463.86	67588.63	1124.775	1265119	0.005376	0.996589
c_fidaxomicin	3550.23	3944.7	4339.17	Decrease	66700.62	67499.82	799.1962	638714.6	0.002714	0.999303
c_vancPO	9.7	313.7	8227.7	Decrease	66820.86	67110.95	290.0954	84155.34	0.000358	0.999661
eff_vanc	0.31	0.585	0.85	Increase	66940.67	67222.72	282.0488	79551.54	0.000338	0.999999
eff_FMTcolonoscopy	0.8	0.87	0.9999	Increase	67085.61	67100.22	14.606	213.3352	9.07E-07	1
c_FMTcolonoscopy	4814.1	5349	5883.9	Decrease	67100.01	67100.43	0.42792	0.183116	7.78E-10	1
c_FMTpill	2050	2050	6150	Increase	67100.22	67100.22	0	0	0	1
p_Initial_NS	0.459	0.51	0.561	Increase	67100.22	67100.22	0	0	0	1
p_Initial_severe	0.423	0.47	0.517	Increase	67100.22	67100.22	0	0	0	1
eff_FMTpill	0.68	0.733	0.91	Increase	67100.22	67100.22	0	0	0	1
eff_FMTenema	0	0.621	0.621	Increase	67100.22	67100.22	0	0	0	1
eff_metronidizole	0	0.75	0.75	Increase	67100.22	67100.22	0	0	0	1
c_metroPO	25	64.6	454	Increase	67100.22	67100.22	0	0	0	1
c_FMTenema	100	1600	3500	Increase	67100.22	67100.22	0	0	0	1
c_rifaximin	1940.4	2156	2371.6	Increase	67100.22	67100.22	0	0	0	1
p_fulminant	0.018	0.02	0.022	Increase	67100.22	67100.22	0	0	0	1
eff_rifaximin	0	0.85	0.85	Increase	67100.22	67100.22	0	0	0	1
eff_vancpulsetaper	0.549	0.61	0.671	Increase	67100.22	67100.22	0	0	0	1
c_metroIV	43.74	48.6	53.46	Increase	67100.22	67100.22	0	0	0	1

*Note: Gray cells denote variables that do not contribute to the model results.

Table 46. 1-way Sensitivity Analysis, varying Effectiveness of Fidaxomicin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
0.0%	VANC	2	2468.64	0.00	0.6459	0.0000	0.00	-2468.64	3822.17	
0.0%	FMT	1	5572.59	3103.95	0.7167	0.0708	43817.73	-5572.59	7775.22	
0.0%	FIDA	0	6905.09	1332.50	0.5804	-0.1363	-9773.02	-6905.09	11897.79	(Dominated)
22.0%	VANC	2	2262.72	0.00	0.6543	0.0000	0.00	-2262.72	3458.27	
22.0%	FMT	1	5572.59	3309.87	0.7167	0.0624	53025.60	-5572.59	7775.22	
22.0%	FIDA	0	5913.57	340.98	0.6194	-0.0973	-3504.05	-5913.57	9547.25	(Dominated)
44.0%	VANC	2	2059.56	0.00	0.6636	0.0000	0.00	-2059.56	3103.40	
44.0%	FIDA	0	5141.66	3082.11	0.6507	-0.0129	-238668.52	-5141.66	7901.37	(Dominated)
44.0%	FMT	1	5572.59	3513.03	0.7167	0.0531	66199.01	-5572.59	7775.22	
66.0%	VANC	2	1848.32	0.00	0.6721	0.0000	0.00	-1848.32	2749.92	
66.0%	FIDA	0	4472.96	2624.63	0.6795	0.0074	354271.71	-4472.96	6582.26	
66.0%	FMT	1	5572.59	1099.63	0.7167	0.0372	29588.02	-5572.59	7775.22	
88.0%	VANC	2	1643.88	0.00	0.6805	0.0000	0.00	-1643.88	2415.87	
88.0%	FIDA	0	3995.26	2351.37	0.7070	0.0266	88537.95	-3995.26	5650.92	
88.0%	FMT	1	5572.59	1577.33	0.7167	0.0097	162585.69	-5572.59	7775.22	

Table 47. 1-way Sensitivity Analysis, varying Probability of Death from CDI

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
7.7%	VANC	2	1705.25	0.00	0.6896	0.0000	0.00	-1705.25	2472.75	
7.7%	FIDA	0	4018.64	2313.39	0.7135	0.0239	96834.51	-4018.64	5632.22	
7.7%	FMT	1	5626.61	1607.97	0.7246	0.0111	145341.42	-5626.61	7765.42	
8.2%	VANC	2	1685.70	0.00	0.6863	0.0000	0.00	-1685.70	2456.32	
8.2%	FIDA	0	4013.11	2327.41	0.7109	0.0247	94310.68	-4013.11	5644.75	
8.2%	FMT	1	5604.15	1591.04	0.7216	0.0107	149083.93	-5604.15	7766.09	
8.6%	VANC	2	1663.70	0.00	0.6822	0.0000	0.00	-1663.70	2438.82	
8.6%	FIDA	0	4005.90	2342.19	0.7077	0.0255	91723.17	-4005.90	5660.34	
8.6%	FMT	1	5580.61	1574.72	0.7183	0.0106	148046.99	-5580.61	7768.66	
9.0%	VANC	2	1642.33	0.00	0.6786	0.0000	0.00	-1642.33	2420.14	
9.0%	FIDA	0	3998.72	2356.39	0.7051	0.0265	89004.25	-3998.72	5671.27	
9.0%	FMT	1	5560.82	1562.10	0.7155	0.0105	149306.96	-5560.82	7771.43	
9.5%	VANC	2	1618.22	0.00	0.6742	0.0000	0.00	-1618.22	2400.08	
9.5%	FIDA	0	3990.64	2372.42	0.7021	0.0278	85210.37	-3990.64	5684.03	
9.5%	FMT	1	5537.28	1546.65	0.7123	0.0102	151644.19	-5537.28	7774.05	

Table 48. 1-way Sensitivity Analysis, varying Cost of Fidaxomicin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
$3,550.23	VANC	2	1494.47	0.00	0.6832	0.0000	0.00	-1494.47	2187.55	
$3,550.23	FIDA	0	3604.13	2109.65	0.7078	0.0247	85556.08	-3604.13	5091.80	
$3,550.23	FMT	1	5583.82	1979.69	0.7178	0.0100	198699.82	-5583.82	7779.16	
$3,747.47	VANC	2	1558.22	0.00	0.6832	0.0000	0.00	-1558.22	2280.86	
$3,747.47	FIDA	0	3803.59	2245.37	0.7078	0.0247	91060.04	-3803.59	5373.60	
$3,747.47	FMT	1	5583.82	1780.23	0.7178	0.0100	178679.85	-5583.82	7779.16	
$3,944.70	VANC	2	1621.97	0.00	0.6832	0.0000	0.00	-1621.97	2374.17	
$3,944.70	FIDA	0	4003.05	2381.09	0.7078	0.0247	96564.01	-4003.05	5655.40	
$3,944.70	FMT	1	5583.82	1580.77	0.7178	0.0100	158659.88	-5583.82	7779.16	

$4,141.94	VANC	2	1685.71	0.00	0.6832	0.0000	0.00	-1685.71	2467.48	
$4,141.94	FIDA	0	4202.52	2516.81	0.7078	0.0247	102067.97	-4202.52	5937.19	
$4,141.94	FMT	1	5583.82	1381.30	0.7178	0.0100	138639.92	-5583.82	7779.16	
$4,339.17	VANC	2	1749.46	0.00	0.6832	0.0000	0.00	-1749.46	2560.79	
$4,339.17	FIDA	0	4401.98	2652.52	0.7078	0.0247	107571.93	-4401.98	6218.99	
$4,339.17	FMT	1	5583.82	1181.84	0.7178	0.0100	118619.95	-5583.82	7779.16	

Table 49. 1-way Sensitivity Analysis, varying Cost of Vancomycin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
$9.70	VANC	2	1354.52	0.00	0.6821	0.0000	0.00	-1354.52	1985.76	
$9.70	FIDA	0	3987.15	2632.63	0.7079	0.0258	102042.44	-3987.15	5632.24	
$9.70	FMT	1	5576.33	1589.18	0.7180	0.0101	156881.27	-5576.33	7765.98	
$2,064.20	VANC	2	3433.47	0.00	0.6821	0.0000	0.00	-3433.47	5033.55	
$2,064.20	FIDA	0	4056.80	623.33	0.7079	0.0258	24160.66	-4056.80	5730.62	
$2,064.20	FMT	1	5576.33	1519.53	0.7180	0.0101	150005.79	-5576.33	7765.98	
$4,118.70	FIDA	0	4126.45	0.00	0.7079	0.0000	0.00	-4126.45	5829.00	
$4,118.70	VANC	2	5512.42	1385.97	0.6821	-0.0258	-53721.13	-5512.42	8081.34	(Dominated)
$4,118.70	FMT	1	5576.33	1449.89	0.7180	0.0101	143130.30	-5576.33	7765.98	
$6,173.20	FIDA	0	4196.09	0.00	0.7079	0.0000	0.00	-4196.09	5927.39	
$6,173.20	FMT	1	5576.33	1380.24	0.7180	0.0101	136254.82	-5576.33	7765.98	
$6,173.20	VANC	2	7591.37	2015.03	0.6821	-0.0359	-56083.41	-7591.37	11129.13	(Dominated)
$8,227.70	FIDA	0	4265.74	0.00	0.7079	0.0000	0.00	-4265.74	6025.77	
$8,227.70	FMT	1	5576.33	1310.59	0.7180	0.0101	129379.34	-5576.33	7765.98	
$8,227.70	VANC	2	9670.31	4093.98	0.6821	-0.0359	-113945.76	-9670.31	14176.92	(Dominated)

Table 50. 1-way Sensitivity Analysis, varying Effectiveness of Vancomycin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
31.0%	VANC	2	2748.16	0.00	0.6559	0.0000	0.00	-2748.16	4189.96	
31.0%	FIDA	0	4036.92	1288.76	0.7056	0.0497	25911.44	-4036.92	5721.04	
31.0%	FMT	1	5586.50	1549.57	0.7160	0.0103	149765.12	-5586.50	7802.65	
44.5%	VANC	2	2217.80	0.00	0.6684	0.0000	0.00	-2217.80	3318.18	
44.5%	FIDA	0	4014.30	1796.49	0.7060	0.0376	47807.66	-4014.30	5686.32	
44.5%	FMT	1	5586.50	1572.20	0.7160	0.0100	156953.02	-5586.50	7802.65	
58.0%	VANC	2	1669.73	0.00	0.6805	0.0000	0.00	-1669.73	2453.68	
58.0%	FIDA	0	3997.73	2327.99	0.7062	0.0257	90639.71	-3997.73	5661.02	
58.0%	FMT	1	5586.50	1588.77	0.7160	0.0098	162302.82	-5586.50	7802.65	
71.5%	VANC	2	1146.73	0.00	0.6930	0.0000	0.00	-1146.73	1654.62	
71.5%	FIDA	0	3981.16	2834.43	0.7066	0.0135	209736.93	-3981.16	5634.56	
71.5%	FMT	1	5586.50	1605.34	0.7160	0.0094	170545.78	-5586.50	7802.65	
85.0%	VANC	2	588.95	0.00	0.7044	0.0000	0.00	-588.95	836.16	
85.0%	FIDA	0	3965.38	3376.43	0.7069	0.0026	1309819.72	-3965.38	5609.27	
85.0%	FMT	1	5586.50	1621.11	0.7160	0.0090	179311.53	-5586.50	7802.65	

C. Fulminant CDI

1. Status Quo Scenario

CE was conducted at the second episode of CDI/first rCDI for fulminant cases, as the status quo treatment option only offers vancomycin at a higher dose with metronidazole via IV.

Table 51. Status Quo Scenario. Cost Effectiveness Rankings: Initial, fulminant CDI

Strategy	Cost	Incr Cost	Eff	Incr Eff	Incr C/E	NMB	C/E	Dominance
Vancomycin pulse taper	$1,457.92		0.5129			-1457.92	2842.44	
Fidaxomicin	$4,334.20	2876.29	0.5999	0.0870	33071.92	-4334.20	7225.10	

Figure 25. Cost Effectiveness Analysis with WTP $100,000

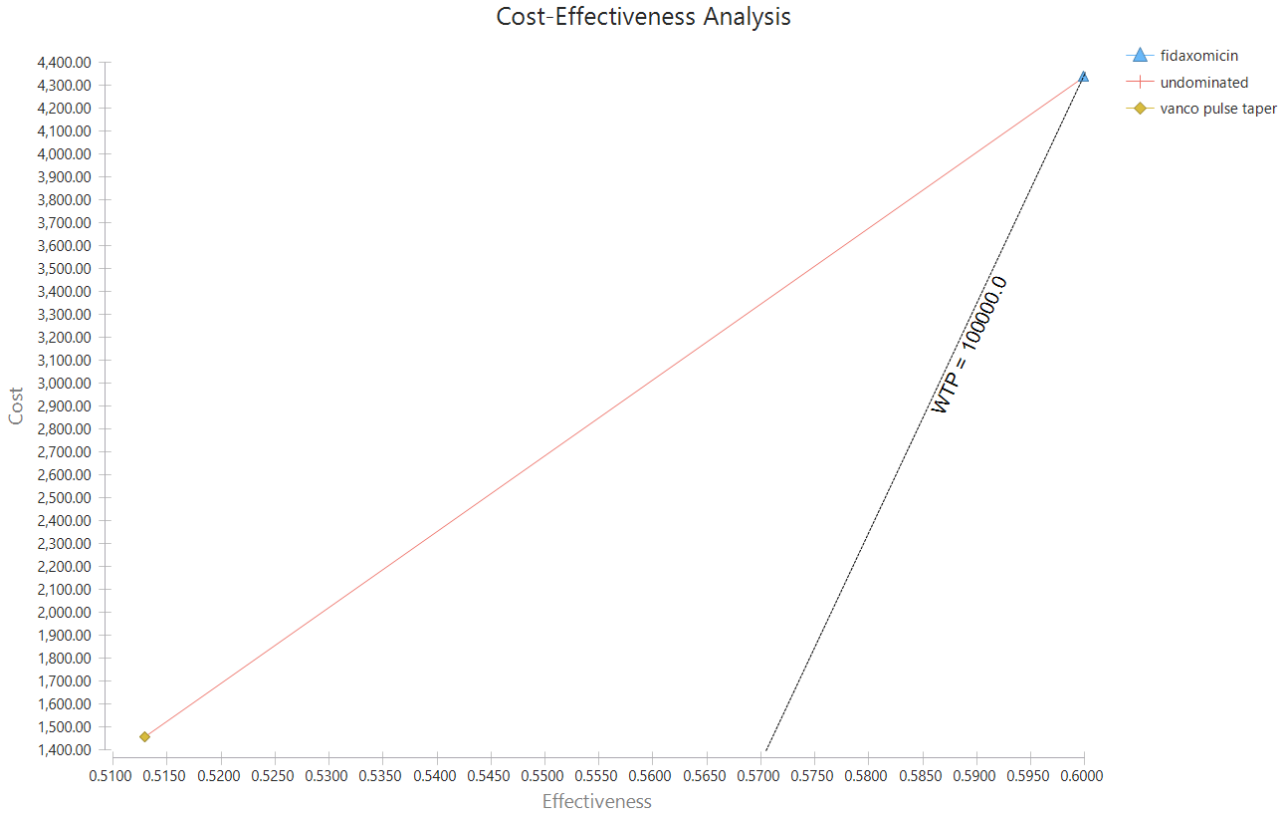


Figure 26. Tornado Diagram NMB

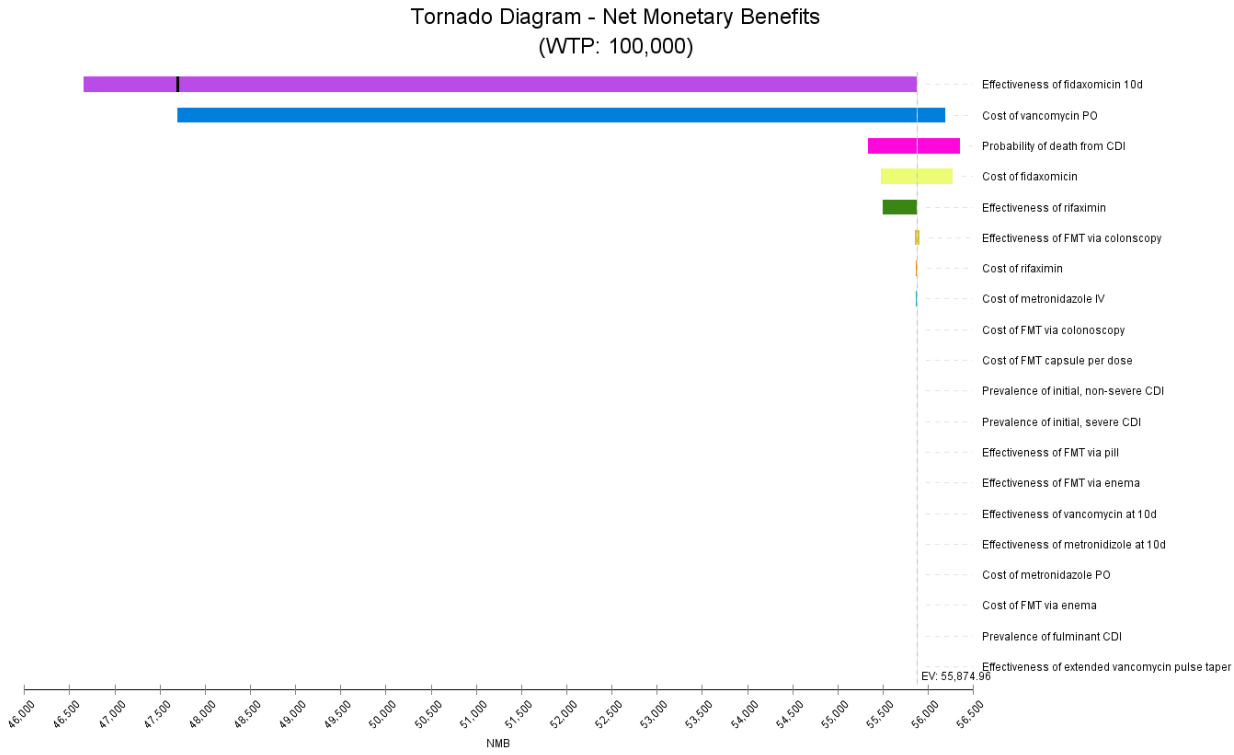


Table 52. Tornado Diagram NMB Report

Variable Name	Variable Low	Variable Base	Variable High	Impact	Low	High	Spread	Spread²	Risk %	Cum Risk %
eff_fidaxomicin	0	0.88	0.88	Increase	46719.86	55928.77	9208.915	84804114	0.534278	0.534278
c_vancPO	9.7	313.7	8227.7	Decrease	47748.86	56242.98	8494.125	72150156	0.454556	0.988834
p_Death	0.0774	0.086	0.0946	Decrease	55430.53	56415.19	984.6598	969554.8	0.006108	0.994943
c_fidaxomicin	3550.23	3944.7	4339.17	Decrease	55534.3	56323.24	788.94	622426.3	0.003921	0.998864
eff_rifaximin	0	0.85	0.85	Increase	55505.64	55928.77	423.1323	179040.9	0.001128	0.999992
eff_FMTcolonoscopy	0.8	0.87	1	Increase	55922.66	55953.2	30.535	932.3862	5.87E-06	0.999998
c_rifaximin	1940.4	2156	2371.6	Decrease	55921.53	55936.01	14.48832	209.9114	1.32E-06	0.999999
c_metroIV	43.74	48.6	53.46	Decrease	55923.91	55933.63	9.72	94.4784	5.95E-07	1
c_FMTcolonoscopy	4814.1	5349	5883.9	Decrease	55927.65	55929.89	2.24658	5.047122	3.18E-08	1
c_FMTpill	2050	2050	6150	Increase	55928.77	55928.77	0	0	0	1
p_Initial_NS	0.459	0.51	0.561	Increase	55928.77	55928.77	0	0	0	1
p_Initial_severe	0.423	0.47	0.517	Increase	55928.77	55928.77	0	0	0	1
eff_FMTpill	0.68	0.733	0.91	Increase	55928.77	55928.77	0	0	0	1
eff_FMTenema	0	0.621	0.621	Increase	55928.77	55928.77	0	0	0	1
eff_vanc	0.31	0.585	0.85	Increase	55928.77	55928.77	0	0	0	1
eff_metronidizole	0	0.75	0.75	Increase	55928.77	55928.77	0	0	0	1
c_metroPO	25	64.6	454	Increase	55928.77	55928.77	0	0	0	1
c_FMTenema	100	1600	3500	Increase	55928.77	55928.77	0	0	0	1
p_fulminant	0.018	0.02	0.022	Increase	55928.77	55928.77	0	0	0	1
eff_vancpulsetaper	0.549	0.61	0.671	Increase	55928.77	55928.77	0	0	0	1

*Note: Gray cells denote variables that do not contribute to the model results.

Table 53. 1-way Sensitivity Analysis, varying Effectiveness of Fidaxomicin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
0.0%	VANC pulse taper	1	3329.90	0.00	0.5025	0.0000	0.00	-3329.90	6626.58	
0.0%	FIDA	0	6877.43	3547.53	0.5118	0.0093	381829.23	-6877.43	13437.79	
22.0%	VANC pulse taper	1	2950.12	0.00	0.5084	0.0000	0.00	-2950.12	5802.75	
22.0%	FIDA	0	6245.96	3295.83	0.5353	0.0269	122706.50	-6245.96	11669.01	
44.0%	VANC pulse taper	1	2602.44	0.00	0.5134	0.0000	0.00	-2602.44	5069.03	
44.0%	FIDA	0	5640.00	3037.56	0.5583	0.0449	67711.43	-5640.00	10102.81	
66.0%	VANC pulse taper	1	2274.01	0.00	0.5182	0.0000	0.00	-2274.01	4388.70	
66.0%	FIDA	0	5007.70	2733.69	0.5825	0.0643	42509.47	-5007.70	8597.53	
88.0%	VANC pulse taper	1	1909.21	0.00	0.5241	0.0000	0.00	-1909.21	3642.52	
88.0%	FIDA	0	4399.20	2489.99	0.6045	0.0804	30986.52	-4399.20	7277.38	

Table 54. 1-way Sensitivity Analysis, varying Cost of Vancomycin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominanc
$9.70	VANC pulse taper	1	1317.47	0.00	0.5249	0.0000	0.00	-1317.47	2509.85	
$9.70	FIDA	0	4086.87	2769.40	0.6045	0.0796	34794.97	-4086.87	6760.62	
$2,064.20	VANC pulse taper	1	5426.47	0.00	0.5249	0.0000	0.00	-5426.47	10337.71	
$2,064.20	FIDA	0	6208.76	782.29	0.6045	0.0796	9828.76	-6208.76	10270.70	
$4,118.70	FIDA	0	8330.65	0.00	0.6045	0.0000	0.00	-8330.65	13780.79	
$4,118.70	VANC pulse taper	1	9535.47	1204.82	0.5249	-0.0796	-15137.46	-9535.47	18165.57	(Dominate
$6,173.20	FIDA	0	10452.54	0.00	0.6045	0.0000	0.00	-10452.54	17290.87	
$6,173.20	VANC pulse taper	1	13644.47	3191.93	0.5249	-0.0796	-40103.68	-13644.47	25993.44	(Dominate
$8,227.70	FIDA	0	12574.42	0.00	0.6045	0.0000	0.00	-12574.42	20800.95	
$8,227.70	VANC pulse taper	1	17753.47	5179.05	0.5249	-0.0796	-65069.90	-17753.47	33821.30	(Dominate

Table 55. 1-way Sensitivity Analysis, varying Probability of Death from CDI

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
7.7%	VANC pulse taper	1	2007.65	0.00	0.5286	0.0000	0.00	-2007.65	3797.83	
7.7%	FIDA	0	4431.09	2423.44	0.6100	0.0813	29793.73	-4431.09	7264.41	
8.2%	VANC pulse taper	1	1987.26	0.00	0.5263	0.0000	0.00	-1987.26	3775.79	
8.2%	FIDA	0	4422.08	2434.82	0.6082	0.0819	29718.73	-4422.08	7270.22	
8.6%	VANC pulse taper	1	1959.66	0.00	0.5231	0.0000	0.00	-1959.66	3746.44	
8.6%	FIDA	0	4406.81	2447.16	0.6054	0.0823	29721.32	-4406.81	7279.07	
9.0%	VANC pulse taper	1	1931.86	0.00	0.5198	0.0000	0.00	-1931.86	3716.32	
9.0%	FIDA	0	4392.16	2460.30	0.6029	0.0831	29624.10	-4392.16	7285.29	
9.5%	VANC pulse taper	1	1901.41	0.00	0.5162	0.0000	0.00	-1901.41	3683.18	
9.5%	FIDA	0	4378.12	2476.72	0.6002	0.0840	29488.88	-4378.12	7294.09	

Table 56. 1-way Sensitivity Analysis, varying Cost of Fidaxomicin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
$3,550.23	VANC pulse taper	1	1794.38	0.00	0.5241	0.0000	0.00	-1794.38	3423.46	
$3,550.23	FIDA	0	4013.37	2218.99	0.6039	0.0798	27813.22	-4013.37	6645.50	
$3,747.47	VANC pulse taper	1	1853.57	0.00	0.5241	0.0000	0.00	-1853.57	3536.39	
$3,747.47	FIDA	0	4210.61	2357.04	0.6039	0.0798	29543.50	-4210.61	6972.09	
$3,944.70	VANC pulse taper	1	1912.76	0.00	0.5241	0.0000	0.00	-1912.76	3649.32	
$3,944.70	FIDA	0	4407.84	2495.08	0.6039	0.0798	31273.77	-4407.84	7298.68	
$4,141.94	VANC pulse taper	1	1971.95	0.00	0.5241	0.0000	0.00	-1971.95	3762.25	
$4,141.94	FIDA	0	4605.08	2633.13	0.6039	0.0798	33004.05	-4605.08	7625.27	
$4,339.17	VANC pulse taper	1	2031.14	0.00	0.5241	0.0000	0.00	-2031.14	3875.18	
$4,339.17	FIDA	0	4802.31	2771.17	0.6039	0.0798	34734.32	-4802.31	7951.86	

Table 57. 1-way Sensitivity Analysis, varying Effectiveness of Rifaximin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
0.0%	VANC pulse taper	1	1919.04	0.00	0.5201	0.0000	0.00	-1919.04	3689.48	
0.0%	FIDA	0	4573.37	2654.34	0.5987	0.0785	33802.39	-4573.37	7639.31	
21.3%	VANC pulse taper	1	1919.04	0.00	0.5201	0.0000	0.00	-1919.04	3689.48	
21.3%	FIDA	0	4535.93	2616.89	0.5991	0.0790	33125.44	-4535.93	7570.77	
42.5%	VANC pulse taper	1	1919.04	0.00	0.5201	0.0000	0.00	-1919.04	3689.48	
42.5%	FIDA	0	4496.35	2577.31	0.5997	0.0796	32378.80	-4496.35	7497.21	
63.8%	VANC pulse taper	1	1919.04	0.00	0.5201	0.0000	0.00	-1919.04	3689.48	
63.8%	FIDA	0	4451.95	2532.91	0.6005	0.0803	31532.89	-4451.95	7414.19	
85.0%	VANC pulse taper	1	1919.04	0.00	0.5201	0.0000	0.00	-1919.04	3689.48	
85.0%	FIDA	0	4411.83	2492.80	0.6011	0.0809	30803.42	-4411.83	7340.04	

2. Alternative Scenario

Table 58. Alterative Scenario with FMT. Cost Effectiveness Rankings: Initial, Fulminant CDI

Strategy	Cost	Incr Cost	Eff	Incr Eff	Incr C/E	NMB	C/E	Dominance
Vancomycin & metronidazole IV	$672.42		0.5644			-672.42	1191.42	
FMT	$2,165.84	1493.42	0.5886	0.0242	61593.37	-2165.84	3679.46	

Figure 27. Cost Effectiveness Analysis with WTP $100,000

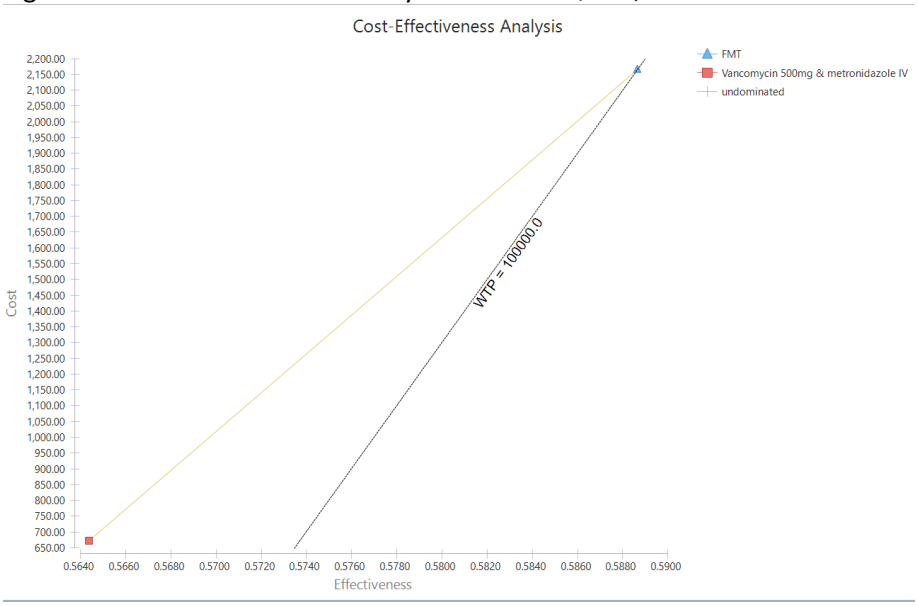


Figure 28. Tornado Diagram NMB

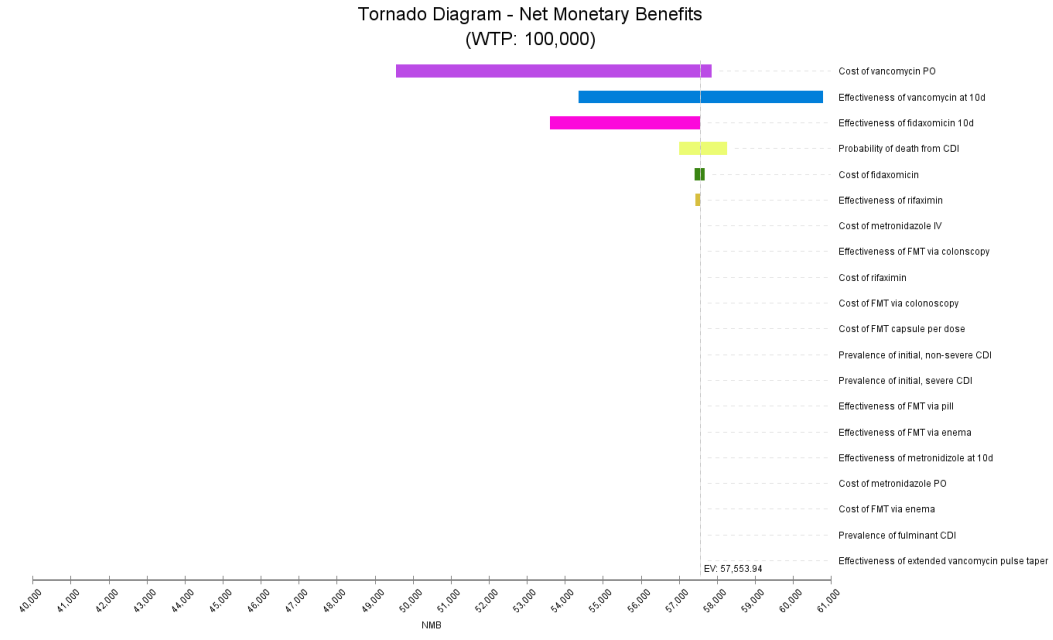


Table 59. Tornado Diagram NMB Report

Variable Name	Variable Low	Variable Base	Variable High	Impact	Low	High	Spread	Spread²	Risk %	Cum Risk %
c_vancPO	9.7	313.7	8227.7	Decrease	49551.3	57861.34	8310.042	69056791	0.541429	0.541429
eff_vanc	0.31	0.585	0.85	Increase	54361.43	60781.05	6419.623	41211557	0.323113	0.864542
eff_fidaxomicin	0	0.88	0.88	Increase	53604.94	57553.94	3948.994	15594556	0.122267	0.986809
p_Death	0.0774	0.086	0.0946	Decrease	57012.53	58276.6	1264.069	1597872	0.012528	0.999337
c_fidaxomicin	3550.23	3944.7	4339.17	Decrease	57421.95	57685.93	263.9793	69685.08	0.000546	0.999883
eff_rifaximin	0	0.85	0.85	Increase	57432.59	57553.94	121.348	14725.34	0.000115	0.999999
c_metroIV	43.74	48.6	53.46	Decrease	57549.08	57558.8	9.72	94.4784	7.41E-07	1
eff_FMTcolonoscopy	0.8	0.87	0.9999	Increase	57547.83	57553.94	6.107	37.29545	2.92E-07	1
c_rifaximin	1940.4	2156	2371.6	Decrease	57551.52	57556.35	4.82944	23.32349	1.83E-07	1
c_FMTcolonoscopy	4814.1	5349	5883.9	Decrease	57553.51	57554.37	0.85584	0.732462	5.74E-09	1
c_FMTpill	2050	2050	6150	Increase	57553.94	57553.94	0	0	0	1
p_Initial_NS	0.459	0.51	0.561	Increase	57553.94	57553.94	0	0	0	1
p_Initial_severe	0.423	0.47	0.517	Increase	57553.94	57553.94	0	0	0	1
eff_FMTpill	0.68	0.733	0.91	Increase	57553.94	57553.94	0	0	0	1
eff_FMTenema	0	0.621	0.621	Increase	57553.94	57553.94	0	0	0	1
eff_metronidizole	0	0.75	0.75	Increase	57553.94	57553.94	0	0	0	1
c_metroPO	25	64.6	454	Increase	57553.94	57553.94	0	0	0	1
c_FMTenema	100	1600	3500	Increase	57553.94	57553.94	0	0	0	1
p_fulminant	0.018	0.02	0.022	Increase	57553.94	57553.94	0	0	0	1
eff_vancpulsetaper	0.549	0.61	0.671	Increase	57553.94	57553.94	0	0	0	1

*Note: Gray cells denote variables that do not contribute to the model results.

Table 60. 1-way Sensitivity Analysis, varying Cost of Vancomycin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
$9.70	VAN & METRO IV	0	1367.44	0.00	0.5974	0.0000	0.00	-1367.44	2289.11	
$9.70	FMT	1	5602.54	4235.10	0.6260	0.0286	148120.78	-5602.54	8950.29	
$2,064.20	VAN & METRO IV	0	3440.64	0.00	0.5974	0.0000	0.00	-3440.64	5759.64	
$2,064.20	FMT	1	5602.54	2161.90	0.6260	0.0286	75611.64	-5602.54	8950.29	
$4,118.70	VAN & METRO IV	0	5513.84	0.00	0.5974	0.0000	0.00	-5513.84	9230.18	
$4,118.70	FMT	1	5602.54	88.71	0.6260	0.0286	3102.50	-5602.54	8950.29	
$6,173.20	FMT	1	5602.54	0.00	0.6260	0.0000	0.00	-5602.54	8950.29	
$6,173.20	VAN & METRO IV	0	7587.03	1984.49	0.5974	-0.0286	-69406.65	-7587.03	12700.72	(Dominated)
$8,227.70	FMT	1	5602.54	0.00	0.6260	0.0000	0.00	-5602.54	8950.29	
$8,227.70	VAN & METRO IV	0	9660.23	4057.68	0.5974	-0.0286	-141915.79	-9660.23	16171.26	(Dominated)

Table 61. 1-way Sensitivity Analysis, varying Efficacy of Vancomycin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance
31.0%	Vancomycin & metronidazole IV	0	2802.39	0.00	0.5797	0.0000	0.00	-2802.39	4834.29	
31.0%	FMT	1	5602.01	2799.62	0.6316	0.0519	53974.69	-5602.01	8870.14	
44.5%	Vancomycin & metronidazole IV	0	2237.45	0.00	0.5902	0.0000	0.00	-2237.45	3791.06	
44.5%	FMT	1	5602.01	3364.56	0.6316	0.0414	81334.67	-5602.01	8870.14	
58.0%	Vancomycin & metronidazole IV	0	1716.96	0.00	0.6001	0.0000	0.00	-1716.96	2861.30	
58.0%	FMT	1	5602.01	3885.05	0.6316	0.0315	123356.08	-5602.01	8870.14	
71.5%	Vancomycin & metronidazole IV	0	1155.73	0.00	0.6104	0.0000	0.00	-1155.73	1893.33	
71.5%	FMT	1	5602.01	4446.28	0.6316	0.0211	210363.48	-5602.01	8870.14	
85.0%	Vancomycin & metronidazole IV	0	622.30	0.00	0.6210	0.0000	0.00	-622.30	1002.09	
85.0%	FMT	1	5602.01	4979.71	0.6316	0.0106	471612.37	-5602.01	8870.14	

Table 62. 1-way Sensitivity Analysis, varying Effectiveness of Fidaxomicin

	Strategy	Index	Cost	Incr Cost	Eff	Incr Eff	ICER	NMB	C/E	Dominance

0.0%	Vancomycin & metronidazole IV	0	2503.78	0.00	0.5682	0.0000	0.00	-2503.78	4406.76	
0.0%	FMT	1	5595.59	3091.81	0.6278	0.0596	51879.46	-5595.59	8913.51	
22.0%	Vancomycin & metronidazole IV	0	2306.42	0.00	0.5751	0.0000	0.00	-2306.42	4010.77	
22.0%	FMT	1	5595.59	3289.17	0.6278	0.0527	62403.99	-5595.59	8913.51	
44.0%	Vancomycin & metronidazole IV	0	2109.39	0.00	0.5820	0.0000	0.00	-2109.39	3624.66	
44.0%	FMT	1	5595.59	3486.20	0.6278	0.0458	76101.01	-5595.59	8913.51	
66.0%	Vancomycin & metronidazole IV	0	1895.20	0.00	0.5890	0.0000	0.00	-1895.20	3217.79	
66.0%	FMT	1	5595.59	3700.39	0.6278	0.0388	95392.40	-5595.59	8913.51	
88.0%	Vancomycin & metronidazole IV	0	1678.66	0.00	0.5972	0.0000	0.00	-1678.66	2811.01	
88.0%	FMT	1	5595.59	3916.93	0.6278	0.0306	128028.33	-5595.59	8913.51	

Table 63. 1-way Sensitivity Analysis, varying Probability of Death from CDI

	Strategy	**Index**	**Cost**	**Incr Cost**	**Eff**	**Incr Eff**	**ICER**	**NMB**	**C/E**	**Dominance**
7.7%	Vancomycin & metronidazole IV	0	1745.54	0.00	0.6047	0.0000	0.00	-1745.54	2886.81	
7.7%	FMT	1	5654.43	3908.89	0.6351	0.0304	128567.81	-5654.43	8903.74	
8.2%	Vancomycin & metronidazole IV	0	1722.88	0.00	0.6014	0.0000	0.00	-1722.88	2864.77	
8.2%	FMT	1	5628.75	3905.88	0.6323	0.0309	126252.08	-5628.75	8901.47	
8.6%	Vancomycin & metronidazole IV	0	1705.18	0.00	0.5985	0.0000	0.00	-1705.18	2848.90	
8.6%	FMT	1	5608.96	3903.78	0.6301	0.0316	123718.46	-5608.96	8901.82	
9.0%	Vancomycin & metronidazole IV	0	1676.09	0.00	0.5938	0.0000	0.00	-1676.09	2822.51	
9.0%	FMT	1	5572.59	3896.50	0.6259	0.0321	121345.45	-5572.59	8902.76	
9.5%	Vancomycin & metronidazole IV	0	1654.09	0.00	0.5903	0.0000	0.00	-1654.09	2802.12	
9.5%	FMT	1	5546.91	3892.82	0.6230	0.0327	119008.25	-5546.91	8903.40	

Table 64. 1-way Sensitivity Analysis, varying Cost of Fidaxomicin

	Strategy	**Index**	**Cost**	**Incr Cost**	**Eff**	**Incr Eff**	**ICER**	**NMB**	**C/E**	**Dominance**

$3,550	Vancomycin & metronidazole IV	0	1568	0	0.5981	0.0000	0.00	-1567.88	2621.40	
$3,550	FMT	1	5580	4012	0.6291	0.0310	129406.59	-5579.54	8868.98	
$3,747	Vancomycin & metronidazole IV	0	1633	0	0.5981	0.0000	0.00	-1633.22	2730.65	
$3,747	FMT	1	5580	3946	0.6291	0.0310	127298.75	-5579.54	8868.98	
$3,945	Vancomycin & metronidazole IV	0	1699	0	0.5981	0.0000	0.00	-1698.57	2839.90	
$3,945	FMT	1	5580	3881	0.6291	0.0310	125190.91	-5579.54	8868.98	
$4,142	Vancomycin & metronidazole IV	0	1764	0	0.5981	0.0000	0.00	-1763.91	2949.16	
$4,142	FMT	1	5580	3816	0.6291	0.0310	123083.07	-5579.54	8868.98	
$4,339	Vancomycin & metronidazole IV	0	1829	0	0.5981	0.0000	0.00	-1829.26	3058.41	
$4,339	FMT	1	5580	3750	0.6291	0.0310	120975.23	-5579.54	8868.98	

D. All CDI Stages

1. Status Quo Scenario

Figure 29. Status Quo Scenario. All CDI Stages: Tornado Diagram NMB

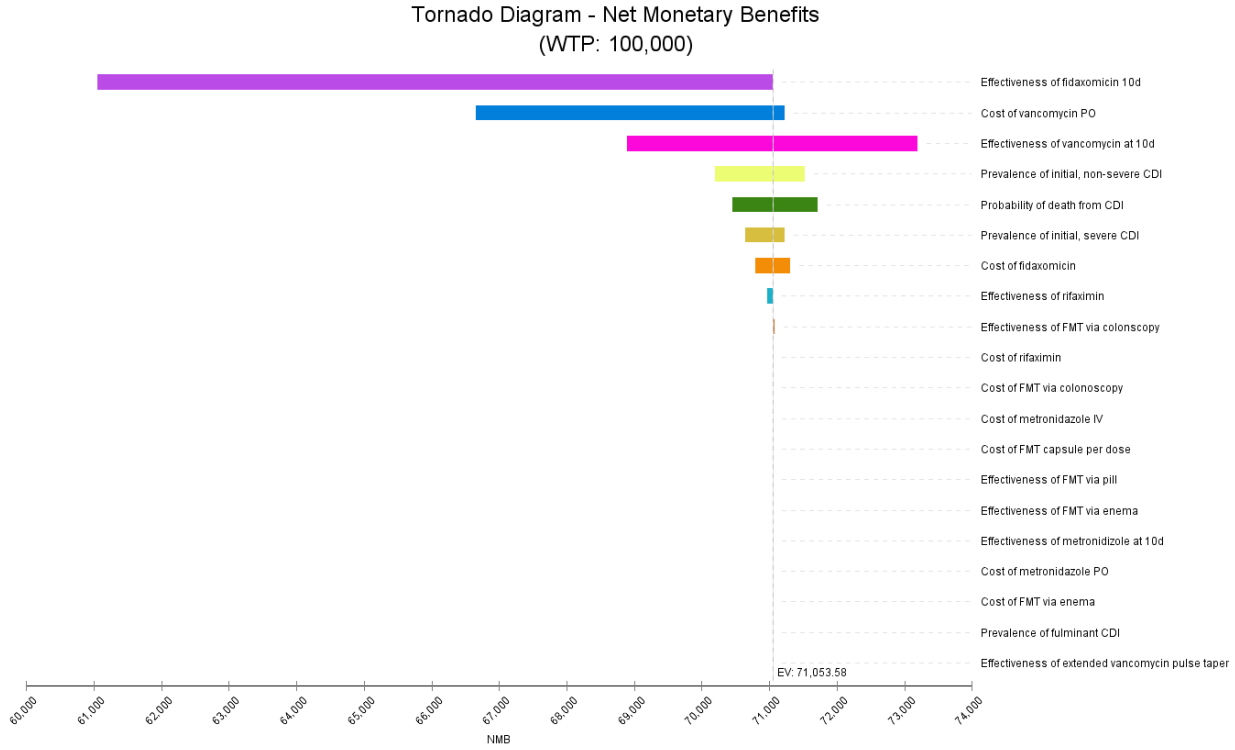


Table 65. Status Quo Scenario. All CDI Stages: Tornado Diagram NMB Report

Variable Name	Variable Low	Variable Base	Variable High	Impact	Low	High	Spread	Spread²	Risk %	Cum Risk %
eff_fidaxomicin	0	0.88	0.88	Increase	61,049.83	71,053.58	10,003.8	100,075,036.1	69.72%	69.72%
c_vancPO	9.7	313.7	8227.7	Decrease	66,650.23	71,222.72	4,572.5	20,907,712.4	14.57%	84.29%
eff_vanc	0.31	0.585	0.85	Increase	68,890.26	73,201.65	4,311.4	18,588,061.6	12.95%	97.24%
p_Initial_NS	0.459	0.51	0.561	Increase	70,199.83	71,529.67	1,329.8	1,768,470.6	1.23%	98.47%
p_Death	0.0774	0.086	0.0946	Decrease	70,461.87	71,723.47	1,261.6	1,591,634.9	1.11%	99.58%
p_Initial_severe	0.423	0.47	0.517	Increase	70,645.98	71,225.65	579.7	336,016.4	0.23%	99.81%
c_fidaxomicin	3550.23	3944.7	4339.17	Decrease	70,798.04	71,309.12	511.1	261,198.0	0.18%	99.99%
eff_rifaximin	0	0.85	0.85	Increase	70,970.69	71,053.58	82.9	6,870.7	0.00%	100.00%
eff_FMTcolonoscopy	0.8	0.87	0.9999	Increase	71,053.58	71,077.10	23.5	553.2	0.00%	100.00%
c_rifaximin	1940.4	2156	2371.6	Decrease	71,052.39	71,054.76	2.4	5.6	0.00%	100.00%
c_FMTcolonoscopy	4814.1	5349	5883.9	Decrease	71,052.94	71,054.22	1.3	1.6	0.00%	100.00%
c_metroIV	43.74	48.6	53.46	Decrease	71,053.47	71,053.68	0.2	0.0	0.00%	100.00%
c_FMTpill	2050	2050	6150	Increase	71,053.58	71,053.58	0.0	0.0	0.00%	100.00%
eff_FMTpill	0.68	0.733	0.91	Increase	71,053.58	71,053.58	0.0	0.0	0.00%	100.00%
eff_FMTenema	0	0.621	0.621	Increase	71,053.58	71,053.58	0.0	0.0	0.00%	100.00%
eff_metronidizole	0	0.75	0.75	Increase	71,053.58	71,053.58	0.0	0.0	0.00%	100.00%
c_metroPO	25	64.6	454	Increase	71,053.58	71,053.58	0.0	0.0	0.00%	100.00%
c_FMTenema	100	1600	3500	Increase	71,053.58	71,053.58	0.0	0.0	0.00%	100.00%
p_fulminant	0.018	0.02	0.022	Increase	71,053.58	71,053.58	0.0	0.0	0.00%	100.00%
eff_vancpulsetaper	0.549	0.61	0.671	Increase	71,053.58	71,053.58	0.0	0.0	0.00%	100.00%

*Note: Gray cells denote variables that do not contribute to the model results.

Figure 30. Status Quo Scenario For All CDI Stages: Tornado Diagram Cost

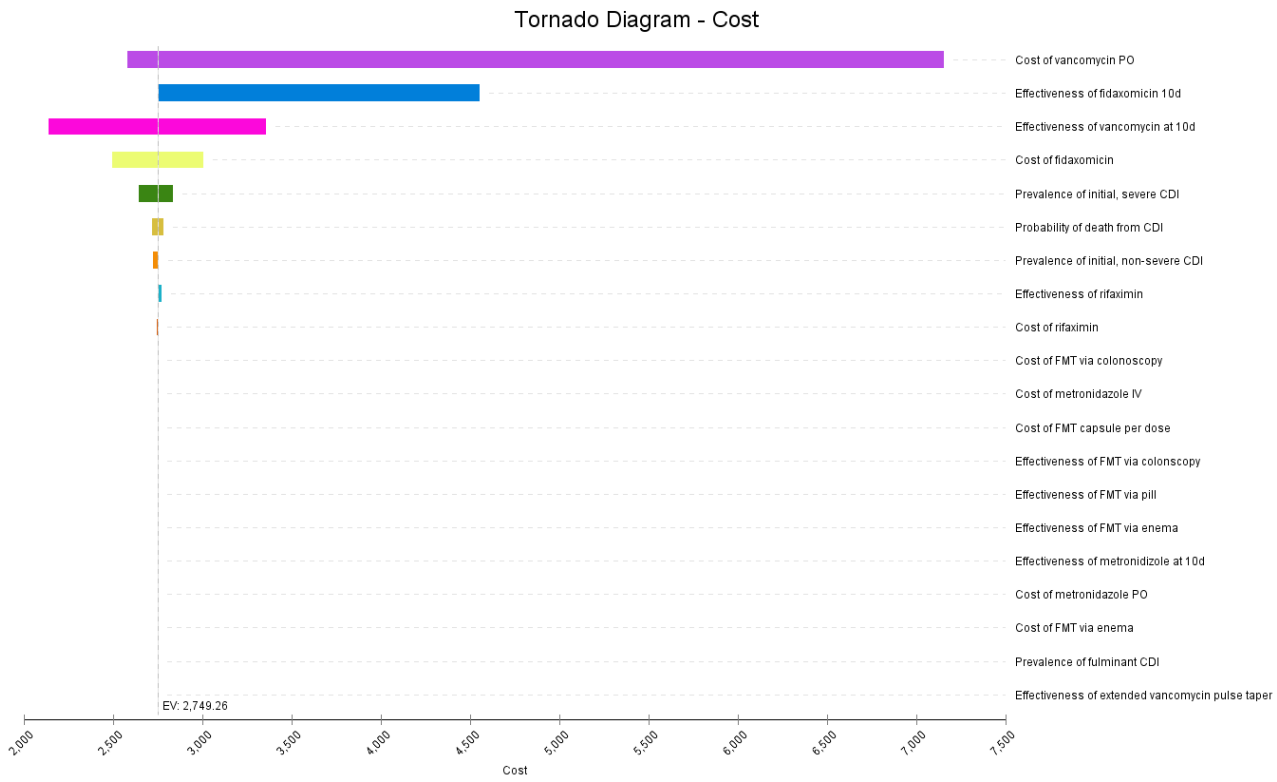


Table 66. Status Quo Scenario For All CDI Stages: Tornado Diagram Cost Report

Variable Name	Variable Low	Variable Base	Variable High	Impact	Low	High	Spread	Spread²	Risk %	Cum Risk %
c_vancPO	9.7	313.7	8227.7	Increase	2,580.11	7,152.61	4572.4952	20907712.3540	80.52%	80.52%
eff_fidaxomicin	0	0.88	0.88	Decrease	2,749.26	4,555.93	1806.6751	3264074.9170	12.57%	93.09%
eff_vanc	0.31	0.585	0.85	Decrease	2,138.09	3,359.38	1221.2854	1491538.1015	5.74%	98.84%
c_fidaxomicin	3550.23	3944.7	4339.17	Increase	2,493.72	3,004.79	511.0753	261197.9950	1.01%	99.84%
p_Initial_severe	0.423	0.47	0.517	Increase	2,645.24	2,834.39	189.1517	35778.3770	0.14%	99.98%
p_Death	0.0774	0.086	0.0946	Decrease	2,721.66	2,780.88	59.2169	3506.6389	0.01%	99.99%
p_Initial_NS	0.459	0.51	0.561	Decrease	2,721.92	2,757.10	35.1746	1237.2553	0.00%	100.00%
eff_rifaximin	0	0.85	0.85	Decrease	2,749.26	2,773.33	24.0705	579.3890	0.00%	100.00%
c_rifaximin	1940.4	2156	2371.6	Increase	2,748.07	2,750.44	2.3716	5.6245	0.00%	100.00%
c_FMTcolonoscopy	4814.1	5349	5883.9	Increase	2,748.61	2,749.90	1.2838	1.6480	0.00%	100.00%
c_metroIV	43.74	48.6	53.46	Increase	2,749.15	2,749.36	0.2119	0.0449	0.00%	100.00%
c_FMTpill	2050	2050	6150	Increase	2,749.26	2,749.26	0.0000	0.0000	0.00%	100.00%
eff_FMTcolonoscopy	0.8	0.87	0.9999	Increase	2,749.26	2,749.26	0.0000	0.0000	0.00%	100.00%
eff_FMTpill	0.68	0.733	0.91	Increase	2,749.26	2,749.26	0.0000	0.0000	0.00%	100.00%
eff_FMTenema	0	0.621	0.621	Increase	2,749.26	2,749.26	0.0000	0.0000	0.00%	100.00%
eff_metronidizole	0	0.75	0.75	Increase	2,749.26	2,749.26	0.0000	0.0000	0.00%	100.00%
c_metroPO	25	64.6	454	Increase	2,749.26	2,749.26	0.0000	0.0000	0.00%	100.00%
c_FMTenema	100	1600	3500	Increase	2,749.26	2,749.26	0.0000	0.0000	0.00%	100.00%
p_fulminant	0.018	0.02	0.022	Increase	2,749.26	2,749.26	0.0000	0.0000	0.00%	100.00%
eff_vancpulsetaper	0.549	0.61	0.671	Increase	2,749.26	2,749.26	0.0000	0.0000	0.00%	100.00%

*Note: Gray cells denote variables that do not contribute to the model results.

Figure 31. Status Quo Scenario For All CDI Stages: Tornado Diagram Effectiveness

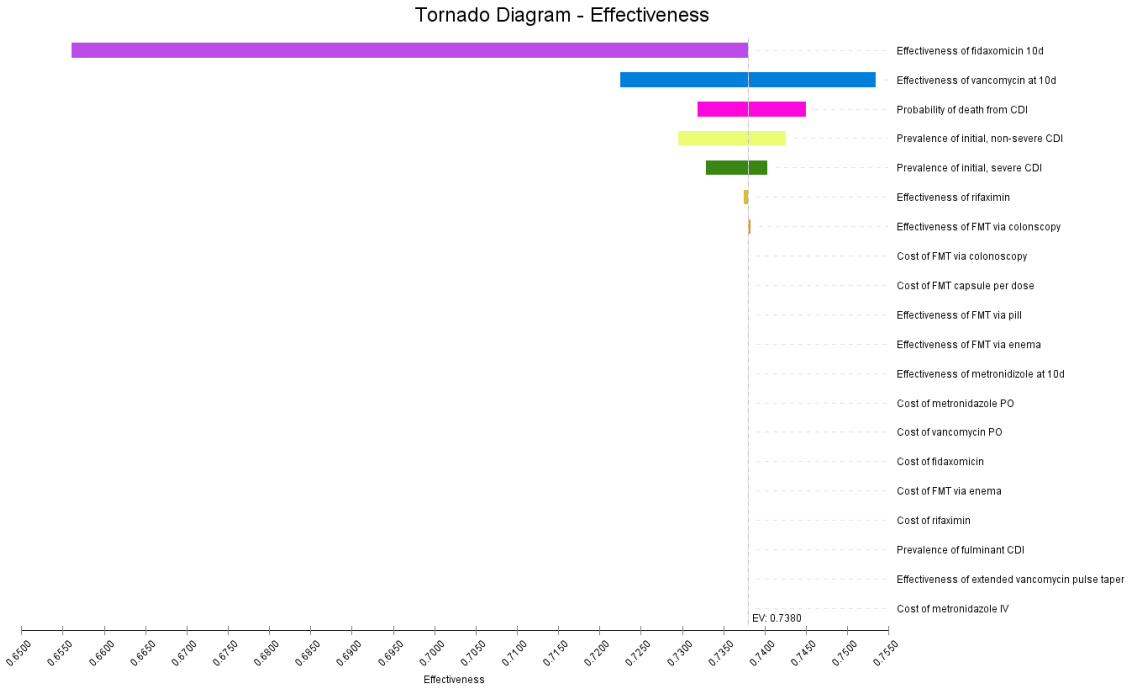


Table 67. Status Quo Scenario For All CDI Stages: Tornado Diagram Effectiveness Report

Variable Name	Variable Low	Variable Base	Variable High	Impact	Low	High	Spread	Spread²	Risk %	Cum Risk %
eff_fidaxomicin	0	0.88	0.88	Increase	0.6561	0.7380	0.0820	0.0067	83.24%	83.24%
eff_vanc	0.31	0.585	0.85	Increase	0.7225	0.7534	0.0309	0.0010	11.83%	95.07%
p_Death	0.0774	0.086	0.0946	Decrease	0.7318	0.7450	0.0132	0.0002	2.16%	97.23%
p_Initial_NS	0.459	0.51	0.561	Increase	0.7296	0.7425	0.0130	0.0002	2.08%	99.31%
p_Initial_severe	0.423	0.47	0.517	Increase	0.7329	0.7403	0.0074	0.0001	0.68%	100.00%
eff_rifaximin	0	0.85	0.85	Increase	0.7374	0.7380	0.0006	0.0000	0.00%	100.00%
eff_FMTcolonoscopy	0.8	0.87	0.9999	Increase	0.7380	0.7383	0.0002	0.0000	0.00%	100.00%
c_FMTcolonoscopy	4814.1	5349	5883.9	Increase	0.7380	0.7380	0.0000	0.0000	0.00%	100.00%
c_FMTpill	2050	2050	6150	Increase	0.7380	0.7380	0.0000	0.0000	0.00%	100.00%
eff_FMTpill	0.68	0.733	0.91	Increase	0.7380	0.7380	0.0000	0.0000	0.00%	100.00%
eff_FMTenema	0	0.621	0.621	Increase	0.7380	0.7380	0.0000	0.0000	0.00%	100.00%
eff_metronidizole	0	0.75	0.75	Increase	0.7380	0.7380	0.0000	0.0000	0.00%	100.00%
c_metroPO	25	64.6	454	Increase	0.7380	0.7380	0.0000	0.0000	0.00%	100.00%
c_vancPO	9.7	313.7	8227.7	Increase	0.7380	0.7380	0.0000	0.0000	0.00%	100.00%
c_fidaxomicin	3550.23	3944.7	4339.17	Increase	0.7380	0.7380	0.0000	0.0000	0.00%	100.00%
c_FMTenema	100	1600	3500	Increase	0.7380	0.7380	0.0000	0.0000	0.00%	100.00%
c_rifaximin	1940.4	2156	2371.6	Increase	0.7380	0.7380	0.0000	0.0000	0.00%	100.00%
p_fulminant	0.018	0.02	0.022	Increase	0.7380	0.7380	0.0000	0.0000	0.00%	100.00%
eff_vancpulsetaper	0.549	0.61	0.671	Increase	0.7380	0.7380	0.0000	0.0000	0.00%	100.00%
c_metroIV	43.74	48.6	53.46	Increase	0.7380	0.7380	0.0000	0.0000	0.00%	100.00%

*Note: Gray cells denote variables that do not contribute to the model results.

2. Alternative Scenario

Figure 32. Alternative Scenario For All CDI Stages: Tornado Diagram NMB

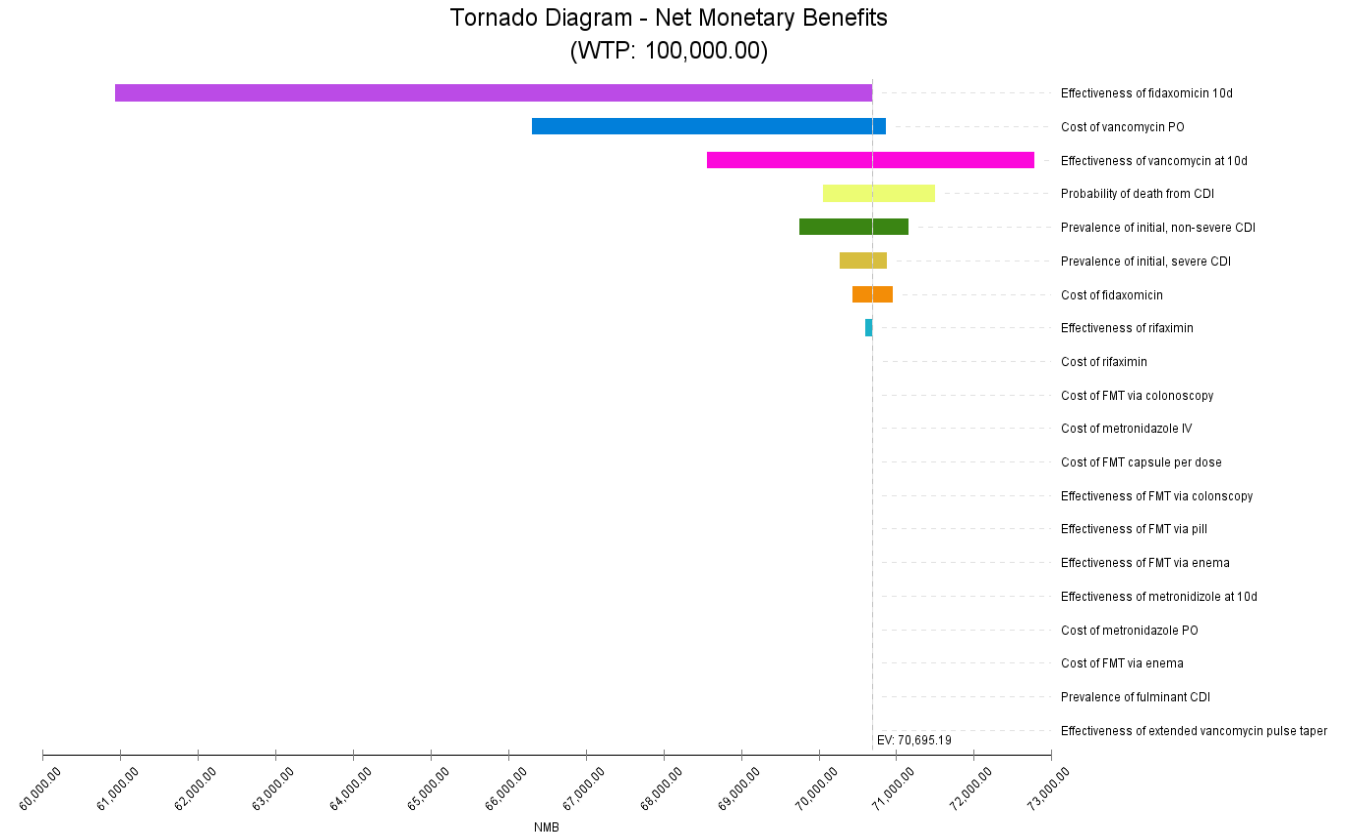


Table 68. Alternative Scenario For All CDI Stages: Tornado Diagram NMB Report

Variable Name	Variable Low	Variable Base	Variable High	Impact	Low	High	Spread	Spread²	Risk %	Cum Risk %
eff_fidaxomicin	0	0.88	0.88	Increase	60,938.95	70,695.19	9,756.2	95,184,131.1	68.77%	68.77%
c_vancPO	9.7	313.7	8227.7	Decrease	66,307.67	70,863.73	4,556.1	20,757,675.4	15.00%	83.76%
eff_vanc	0.31	0.585	0.85	Increase	68,563.91	72,780.47	4,216.6	17,779,328.8	12.84%	96.61%
p_Death	0.0774	0.086	0.0946	Decrease	70,053.05	71,504.12	1,451.1	2,105,628.2	1.52%	98.13%
p_Initial_NS	0.459	0.51	0.561	Increase	69,755.07	71,154.80	1,399.7	1,959,246.8	1.42%	99.54%
p_Initial_severe	0.423	0.47	0.517	Increase	70,276.54	70,876.21	599.7	359,595.4	0.26%	99.80%
c_fidaxomicin	3550.23	3944.7	4339.17	Decrease	70,438.62	70,951.75	513.1	263,298.9	0.19%	99.99%
eff_rifaximin	0	0.85	0.85	Increase	70,603.54	70,695.19	91.6	8,399.0	0.01%	100.00%
c_rifaximin	1940.4	2156	2371.6	Decrease	70,693.77	70,696.61	2.8	8.1	0.00%	100.00%
c_FMTcolonoscopy	4814.1	5349	5883.9	Decrease	70,694.97	70,695.40	0.4	0.2	0.00%	100.00%
c_metroIV	43.74	48.6	53.46	Decrease	70,695.09	70,695.28	0.2	0.0	0.00%	100.00%
c_FMTpill	2050	2050	6150	Increase	70,695.19	70,695.19	0.0	0.0	0.00%	100.00%
eff_FMTcolonoscopy	0.8	0.87	0.9999	Increase	70,695.19	70,695.19	0.0	0.0	0.00%	100.00%
eff_FMTpill	0.68	0.733	0.91	Increase	70,695.19	70,695.19	0.0	0.0	0.00%	100.00%
eff_FMTenema	0	0.621	0.621	Increase	70,695.19	70,695.19	0.0	0.0	0.00%	100.00%
eff_metronidizole	0	0.75	0.75	Increase	70,695.19	70,695.19	0.0	0.0	0.00%	100.00%
c_metroPO	25	64.6	454	Increase	70,695.19	70,695.19	0.0	0.0	0.00%	100.00%
c_FMTenema	100	1600	3500	Increase	70,695.19	70,695.19	0.0	0.0	0.00%	100.00%
p_fulminant	0.018	0.02	0.022	Increase	70,695.19	70,695.19	0.0	0.0	0.00%	100.00%
eff_vancpulsetaper	0.549	0.61	0.671	Increase	70,695.19	70,695.19	0.0	0.0	0.00%	100.00%

*Note: Gray cells denote variables that do not contribute to the model results.

Figure 33. Alternative Scenario For All CDI Stages: Tornado Diagram Cost

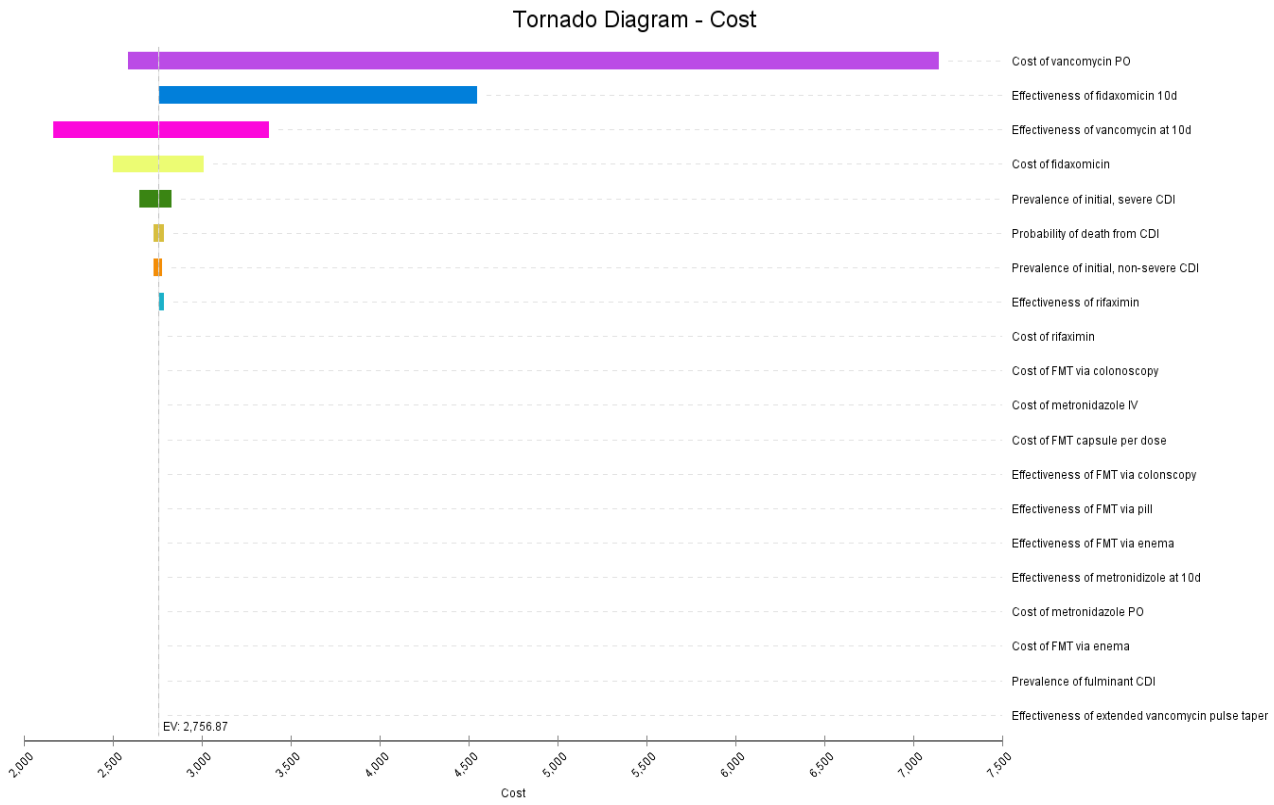


Table 69. Alternative Scenario For All CDI Stages: Tornado Diagram Cost Report

Variable Name	Variable Low	Variable Base	Variable High	Impact	Low	High	Spread	Spread²	Risk %	Cum Risk %
c_vancPO	9.7	313.7	8227.7	Increase	2,588.3372	7,144.3964	4,556.0592	20,757,675.4339	80.62%	80.62%
eff_fidaxomicin	0	0.88	0.88	Decrease	2,756.8748	4,547.4043	1,790.5295	3,205,995.8904	12.45%	93.07%
eff_vanc	0.31	0.585	0.85	Decrease	2,163.4452	3,380.6023	1,217.1571	1,481,471.5035	5.75%	98.82%
c_fidaxomicin	3550.23	3944.7	4339.17	Increase	2,500.3115	3,013.4381	513.1266	263,298.8830	1.02%	99.85%
p_Initial_severe	0.423	0.47	0.517	Increase	2,652.2174	2,831.2402	179.0228	32,049.1558	0.12%	99.97%
p_Death	0.0774	0.086	0.0946	Decrease	2,729.7395	2,790.2643	60.5247	3,663.2417	0.01%	99.99%
p_Initial_NS	0.459	0.51	0.561	Decrease	2,728.2583	2,779.2933	51.0350	2,604.5671	0.01%	100.00%
eff_rifaximin	0	0.85	0.85	Decrease	2,756.8748	2,788.4339	31.5591	995.9768	0.00%	100.00%
c_rifaximin	1940.4	2156	2371.6	Increase	2,755.4518	2,758.2977	2.8459	8.0993	0.00%	100.00%
c_FMTcolonoscopy	4814.1	5349	5883.9	Increase	2,756.6608	2,757.0887	0.4279	0.1831	0.00%	100.00%
c_metroIV	43.74	48.6	53.46	Increase	2,756.7790	2,756.9705	0.1915	0.0367	0.00%	100.00%
c_FMTpill	2050	2050	6150	Increase	2,756.8748	2,756.8748	0.0000	0.0000	0.00%	100.00%
eff_FMTcolonoscopy	0.8	0.87	0.9999	Increase	2,756.8748	2,756.8748	0.0000	0.0000	0.00%	100.00%
eff_FMTpill	0.68	0.733	0.91	Increase	2,756.8748	2,756.8748	0.0000	0.0000	0.00%	100.00%
eff_FMTenema	0	0.621	0.621	Increase	2,756.8748	2,756.8748	0.0000	0.0000	0.00%	100.00%
eff_metronidizole	0	0.75	0.75	Increase	2,756.8748	2,756.8748	0.0000	0.0000	0.00%	100.00%
c_metroPO	25	64.6	454	Increase	2,756.8748	2,756.8748	0.0000	0.0000	0.00%	100.00%
c_FMTenema	100	1600	3500	Increase	2,756.8748	2,756.8748	0.0000	0.0000	0.00%	100.00%
p_fulminant	0.018	0.02	0.022	Increase	2,756.8748	2,756.8748	0.0000	0.0000	0.00%	100.00%
eff_vancpulsetaper	0.549	0.61	0.671	Increase	2,756.8748	2,756.8748	0.0000	0.0000	0.00%	100.00%

*Note: Gray cells denote variables that do not contribute to the model results.

Figure 34. Alternative Scenario For All CDI Stages: Tornado Diagram Effectiveness

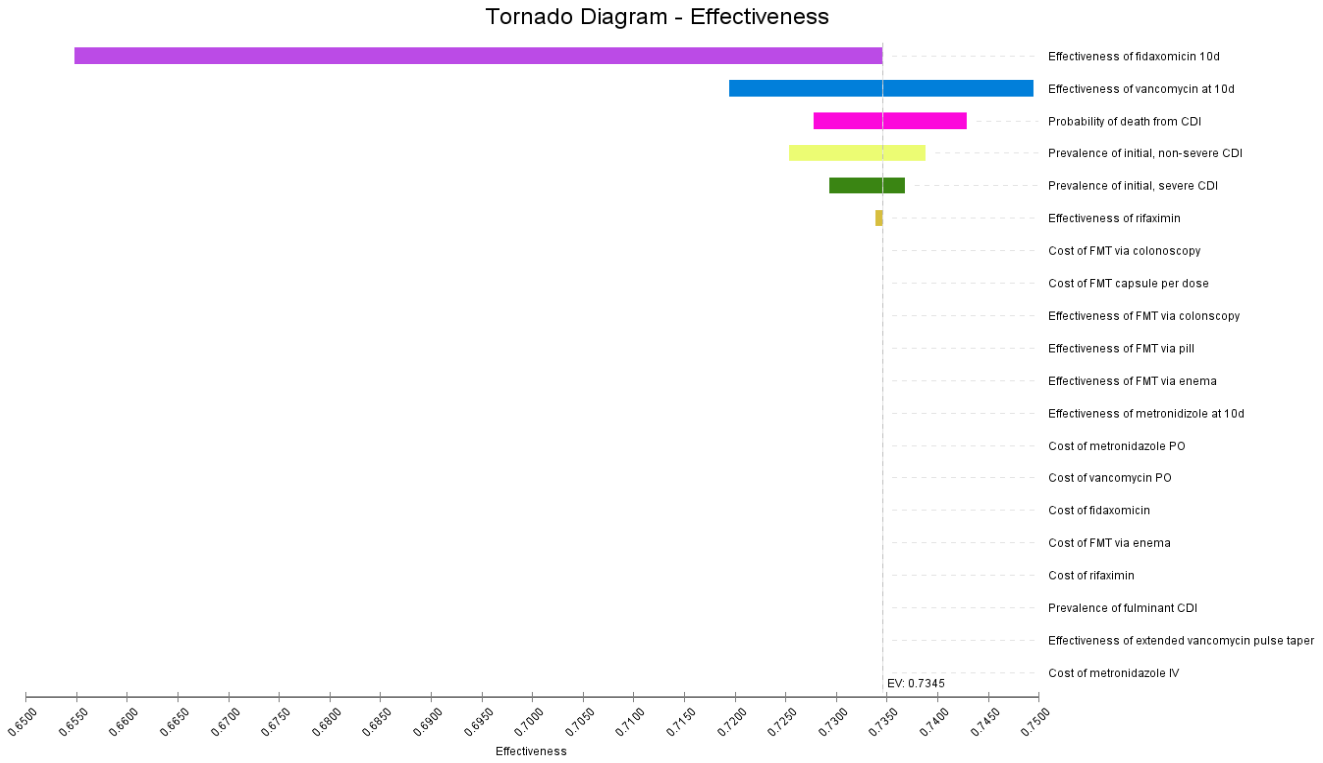


Table 70. Alternative Scenario For All CDI Stages: Tornado Diagram Effectiveness Report

Variable Name	Variable Low	Variable Base	Variable High	Impact	Low	High	Spread	Spread²	Risk %	Cum Risk %
eff_fidaxomicin	0	0.88	0.88	Increase	0.6549	0.7345	0.0797	0.0063	82.28%	82.28%
eff_vanc	0.31	0.585	0.85	Increase	0.7194	0.7494	0.0300	0.0009	11.67%	93.94%
p_Death	0.0774	0.086	0.0946	Decrease	0.7278	0.7429	0.0151	0.0002	2.96%	96.90%
p_Initial_NS	0.459	0.51	0.561	Increase	0.7253	0.7388	0.0135	0.0002	2.36%	99.26%
p_Initial_severe	0.423	0.47	0.517	Increase	0.7293	0.7368	0.0075	0.0001	0.73%	100.00%
eff_rifaximin	0	0.85	0.85	Increase	0.7339	0.7345	0.0006	0.0000	0.00%	100.00%
c_FMTcolonoscopy	4814.1	5349	5883.9	Increase	0.7345	0.7345	0.0000	0.0000	0.00%	100.00%
c_FMTpill	2050	2050	6150	Increase	0.7345	0.7345	0.0000	0.0000	0.00%	100.00%
eff_FMTcolonoscopy	0.8	0.87	0.9999	Increase	0.7345	0.7345	0.0000	0.0000	0.00%	100.00%
eff_FMTpill	0.68	0.733	0.91	Increase	0.7345	0.7345	0.0000	0.0000	0.00%	100.00%
eff_FMTenema	0	0.621	0.621	Increase	0.7345	0.7345	0.0000	0.0000	0.00%	100.00%
eff_metronidizole	0	0.75	0.75	Increase	0.7345	0.7345	0.0000	0.0000	0.00%	100.00%
c_metroPO	25	64.6	454	Increase	0.7345	0.7345	0.0000	0.0000	0.00%	100.00%
c_vancPO	9.7	313.7	8227.7	Increase	0.7345	0.7345	0.0000	0.0000	0.00%	100.00%
c_fidaxomicin	3550.23	3944.7	4339.17	Increase	0.7345	0.7345	0.0000	0.0000	0.00%	100.00%
c_FMTenema	100	1600	3500	Increase	0.7345	0.7345	0.0000	0.0000	0.00%	100.00%
c_rifaximin	1940.4	2156	2371.6	Increase	0.7345	0.7345	0.0000	0.0000	0.00%	100.00%
p_fulminant	0.018	0.02	0.022	Increase	0.7345	0.7345	0.0000	0.0000	0.00%	100.00%
eff_vancpulsetaper	0.549	0.61	0.671	Increase	0.7345	0.7345	0.0000	0.0000	0.00%	100.00%
c_metroIV	43.74	48.6	53.46	Increase	0.7345	0.7345	0.0000	0.0000	0.00%	100.00%

*Note: Gray cells denote variables that do not contribute to the model results.

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APPENDIX J. CURRICULUM VITAE

Nichole M. Persing
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Overview:
My expertise is in quality improvement and patient safety and public health and healthcare analytics. I support the development of healthcare policy through the development of research design, redesign workflows, application of innovation and data driven improvement practices from healthcare and other industries.

Work History:

The MITRE Corporation, Windsor Mill, MD 2015-present

- Support the Center for Medicare and Medicaid Innovation (CMMI) in the development of alternative payment models designed specifically for health insurers currently serving Medicare and Medicaid beneficiaries.
- Serve as the Principal Investigator for the Diagnostic Utilization research work through the FY18-19 MITRE Innovation Program and collaborate with Boston Children's Hospital as external partners.
- Serve as the MITRE Quality Measures lead for selection of quality measures for Advanced Alternative Payment Models (APM) developed by CMMI and serve as an Advanced APM subject matter expert for the Quality Payment Program (QPP) MITRE team.
- Serve as the Health Policy Task Lead in the development of MITRE's health policy modeling and simulation work.
- Served as the MITRE Task Lead for development of complex population health impact model for Value Based Insurance Design Model investments for the Health Plan Innovation team; the financial model helped identify the potential return on investment to Medicare in the Medicare Advantage program.
- Served as the MITRE Task Lead for the development of a complex population health impact model for the Direct Decision Support Model; the financial model helped identify the potential return on investment to Medicare.
- Provided short term support for the development of a Healthcare Payment Learning and Action Network (HCPLAN) economic model, and the Medication Waste Labor and Critical Deterioration Event Models within MITRE's National Patient Safety Project (NPSP)
- Individual Contributor to a research report on disparities in 30-day all-cause hospital readmissions, presented to the Office of the Assistant Secretary for Health.
- Serve as a Subject Matter Expert on Healthcare Leadership & Management, Healthcare Finance & Economics, and Healthcare Quality Improvement and Patient Safety

Johns Hopkins University School of Medicine, Baltimore, MD 2009-2014

- Developed quality improvement and patient safety education projects within the Department of Pediatrics and throughout the organization. These included providing analytic and informatics used to support quality and patient safety initiatives; evaluating quality and patient safety issues, interventions, and training programs; and managing, analyzing, and presenting complex operational, clinical, and administrative quality and patient safety data and informatics across various clinical and operational domains.
- Founded and developed curriculum for a quality and patient safety leadership program designed for resident scholars during their fellowship year.
- Monitored and mentored the pediatric division's quality and safety projects.
- Supported Maintenance of Certification (MOC) Part 4 applications to the American Board of Pediatrics.
- Served as a research assistant and data manager on multiple research grants.

The Institute for Healthcare Improvement, Cambridge, MA 2007-2008

- Developed Research and Development (R&D) projects and provided ongoing research support to R&D activities.
    - Led a Triple Aim focused R&D project on the use of predictive modeling, focusing on identifying resource intensive patients and high-utilizers of healthcare.
    - Supported several Triple Aim focused R&D projects including remote monitoring.
- Managed a year-long, internal organization-wide collaborative on developing and testing methods to achieve better faster improvement results in a rapid and reliable manner.
- Created IHI's first research assistant position and developed standardized research assistant roles and responsibilities, which led to the creation of the Research Assistant Division.
- Within my first year, led IHI's interactive company-wide, annual staff retreat.

National Initiative for Children's Healthcare Quality, Cambridge, MA 2005-2007

- Developed a learning and diffusion network called the Childhood Obesity Action Network through the Accelerating Improvement in Childhood Obesity project [You can still join the Action Network here].
- Coordinated project activities and monthly collaboration calls for the first group of parent partners participating in national collaborative efforts.
- Developed training materials for Learning Collaborative participants for over 15 major educational and quality improvement events.
- Developed systematic communication process and organizational network maps for two of the company's largest and most complex projects, thereby increasing efficiency in communication.
- Streamlined the faculty contracting process during a LEAN rapid improvement event by streamlining processes and developing standard work, decreasing the duration of the contracting process by 50%.

Education:

2010-2021	Johns Hopkins Bloomberg School of Public Health, Baltimore, MD Dr.PH in the Department of Health Policy & Management in Healthcare Leadership and Management
2008-2009	M.P.H. in Comparative Health Systems and Policy with a concentration in Health Economics
2005-2006	Harvard University, Cambridge, MA Non-degree seeking student Coursework in Psychopharmacology of Drug & Alcohol Abuse; Epidemiology
2001-2005	Clark University, Worcester, MA B.A. in Neurobiology

Publications:

Kim JM, Rivera M, **Persing N**, Bundy DG, Psoter KJ, Ghazarian SR, Miller MR, Solomon BS., 2017. Electronic Immunization Alerts and Spillover Effects on Other Preventive Care Services. *Clinical Pediatrics*. 56.9: 811-820.

Rinke, M.L., Mock, C.K., **Persing, N.M.,** Sawyer, M., Haut, E.R., Neufeld, N.J. and Nagy, P., 2015. The Armstrong Institute Resident/Fellow Scholars: A Multispecialty Curriculum to Train Future Leaders in Patient Safety and Quality Improvement. *American Journal of Medical Quality*.

Bundy, D.G., **Persing, N.M.,** Solomon, B.S., King, T.M., Murakami, P.N., Thompson, R.E., Engineer, L.D., Lehmann, C.U. and Miller, M.R., 2013. Improving immunization delivery using an electronic health record: the ImmProve project. *Academic Pediatrics*, *13*(5), pp.458-465.

Posters & Platform Presentations:

1. McFarland, S, Burggraf, K, **Persing, N,** Irshad, A, Abdullah, F, Miller, MR, & Kim, J., September 2017. Pediatric Hospitalist Co-Management of Surgical Patients Improves Safety Outcomes. *American Academy of Pediatrics.* 30-30.
2. Kim JM, Rivera M, **Persing N**, Bundy D, Psoter K, Ghazarian S, Miller M, Solomon B. Electronic Immunization Alerts and Spillover Effects on Other Preventive Care Services. Pediatric Academic Societies Annual Meeting. San Francisco, CA. May 8th, 2017.
3. Kim JM, Rivera M, **Persing N**, Bundy D, Psoter K, Ghazarian S, Miller M, Solomon B. Electronic Immunization Alerts and Spillover Effects on Other Preventive Care Services. 2017 APA Region 4 Conference. Charlottesville, VA. February 11th, 2017.
4. Klaus S, McFarland S, Genies MC, Burggraf K, **Persing N**, Irshad A, Abdullah F, Miller MR, Colantuoni E, Kim JM. "Pediatric Hospitalist Surgical Co-management Improves Safety Outcomes." *Pediatric Academic Societies* Annual Meeting. Baltimore, MD. April 30, 2016.

5. Genies MC, Lopez S, Mirski K, Rinke M, **Persing N**, Bundy D, Milstone A, Lehmann C, Kim G, Miller M, Kim JM. "Missed Vaccination Opportunities during Pediatric Hospitalizations." *Pediatric Academic Societies* Annual Meeting. Baltimore, MD. May 1, 2016.
6. Klaus SA, McFarland S, Burgraff K, Colantuoni E, **Persing N**, Irshad A, Miller M, Abdullah F, Kim J. "Pediatric Hospitalist Surgical Co-Management: A Patient Safety Intervention." American Academy of Pediatrics National Conference and Exhibition, Washington, DC, October 25th, 2015. *Winner of the AAP Section on Hospital Medicine Abstract Research Award.
7. Julia M. Kim, **Nichole Persing**, Sharon Ghazarian, David Bundy, Breanna Dance, Vania Nwokolo, Aditi Vasan, Marlene Miller, Barry Solomon. "Spillover effects of an electronic health record-based immunization reminder system on other childhood preventive health services: Work-in-progress." Oral poster presentation. APA Region IV Meeting, Charlottesville, VA, February 22nd, 2014.
8. King, T., Tomaszewski, K., **Persing, N.**, Arrington-Sanders, R., Land, C., & Willcox, M. (2014). Do Adolescents Want Their Parents to Receive Text Message Reminders for Their Appointments? *Journal of Adolescent Health*,*54*(2), S31-S32.
9. **Persing, N.,** Land, C., Arrington-Sanders, R., Willcox, M., Tomaszewski, K., & King, T. (2014). Variations in Provider Responses to Automated Decision Support and Impact on Missed Opportunities for Vaccine Adolescent Administration. *Journal of Adolescent Health*, *54*(2), S11-S12.

Selected Teaching Experience:

- Co-instructor. Healthcare System: Insurance Fundamentals. MITRE Institute Course. November & December 2018.
- Co-instructor. US Healthcare Reform: The Policy Context. MITRE Institute Course. February, March, & May 2016.
- TIME Patient Safety Course. Second year medical student course, *Johns Hopkins University School of Medicine*, 2014.
- Introduction to Quality Improvement and Patient Safety. Seminar and Workshop series, *Johns Hopkins University School of Medicine.* 2010-2013.
- "Writing Accountability Groups (WAGs): What are they, how do I create one?" Panelist. April 4, 2014.

Leadership Training:

Trusted Advisor Training, 2015
Strengths Finder and Career Anchor Coaching Program, 2015
Analytic Leadership in Patient Safety (ALPS) Fellowship, 2013-14
Lean Sigma Prescription for Healthcare Green Belt Course and Certificate, 2012
Introduction to MS Access Course Series, 2010
IHI Breakthrough Series College Workshop, 2008
Toastmasters International, 2006-2007
LEAN Rapid Improvement Event on Faculty Contracting, 2006
Boston University School of Public Health Leading Environmental Change, 2004
NCAA Leadership Training Series, 2003-2004

Awards:
MITRE Spark Awards: Dec 2018, Jan 2016, Dec 2015, April 2015
Traina Scholarship, 2001-2005