ECONOMIC EVALUATION OF FECAL MICROBIOTA TRANSPLANTATION FOR THE TREATMENT OF RECURRENT *CLOSTRIDIUM DIFFICILE* INFECTION IN AUSTRALIA

Short running title: Econ evaluation of FMT for recurrent CDI

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Acknowledgements

The authors did not receive funding for this research. The authors have no conflicts of interest that are directly relevant to the content of this manuscript. The idea of the paper was developed by Gregory Merlo and Luke Connelly. Costing of FMT developed by David Brain with clinical input from Sam Costello. Further clinical input provided by Simon Goldenberg. The manuscript was prepared by Gregory Merlo. Luke Connelly, David Brain and Nicholas Graves contributed to this paper by reviewing the manuscript and adding content.

THIS ARTICLE HAS BEEN ACCEPTED FOR PUBLICATION AND UNDERGONE FULL PEER REVIEW BUT HAS NOT BEEN THROUGH THE COPYEDITING, TYPESETTING, PAGINATION AND PROOFREADING PROCESS WHICH MAY LEAD TO DIFFERENCES BETWEEN THIS VERSION AND THE VERSION OF RECORD. PLEASE CITE THIS ARTICLE AS DOI: 10.1111/JGH.13402

Abstract

Background and Aim: *Clostridium difficile* is the most common cause of hospital-acquired diarrhoea in Australia. In 2013, a randomised controlled trial demonstrated the effectiveness of faecal microbiota transplantation (FMT) for the treatment of recurrent *Clostridium difficile* infection (CDI). The aim of this study is to evaluate the cost-effectiveness of faecal microbiota transplantation—via either nasoduodenal or colorectal delivery—compared with vancomycin for the treatment of recurrent CDI in Australia

Methods: A Markov model was developed to compare the cost-effectiveness of faecal microbiota transplantation compared with standard antibiotic therapy. A literature review of clinical evidence informed the structure of the model and the choice of parameter values. Clinical effectiveness was measured in terms of quality adjusted life years. Uncertainty in the model was explored using probabilistic sensitivity analysis.

Results: Both nasoduodenal and colorectal FMT resulted in improved quality of life and reduced cost compared with vancomycin. The incremental effectiveness of either FMT delivery compared with vancomycin was 1.2 (95% CI: 0.1, 2.3) QALYs, or 1.4 (95% CI: 0.4, 2.4) life years saved. Treatment with vancomycin resulted in an increased cost of AU$4,094 (95% CI: AU$26, AU$8,161) compared with nasoduodenal delivery of FMT and AU$4,045 (95% CI: -AU$33, AU$8,124) compared with colorectal delivery. The mean difference in cost between colorectal and nasoduodenal FMT was not significant.

Conclusions: If FMT, rather than vancomycin, became standard care for recurrent CDI in Australia, the estimated national healthcare savings would be over AU$4,000 per treated person, with a substantial increase in quality of life.

Keywords: *Clostridium difficile* infection; faecal microbiota transplantation; cost-effectiveness; economic evaluation; vancomycin

INTRODUCTION

Clostridium difficile infection (CDI) is a common bacterial infection that can affect the digestive system.[1] CDI is often successfully treated by stopping treatment of the inciting antibiotic,[1] but CDI and the associated diarrhoea will recur in 15 to 25% of patients and this recurrent CDI can be resistant to further intervention.[2] Up to 65% of patients with recurrent CDI will experience subsequent recurrences after antibiotic therapy is stopped.[3, 4] Recurrent CDI can progress to fulminant colitis,[5] a potentially fatal exacerbation of CDI that can require colectomy.

In the past decade there has been growing interest in the use of faecal microbiota transplantation (FMT) for the treatment of recurrent CDI. FMT involves the infusion of donor faeces to restore a gastrointestinal microbiome more typical of a healthy person.[6, 7] Randomised controlled trials have demonstrated that faecal microbiota transplantation (FMT) is effective for the treatment of recurrent CDI.[8-10] A 2013 trial found a cure without relapse after 10 weeks of 81% for the 16 patients treated with nasoduodenal FMT compared with 31% for the patients who receive standard antibiotic therapy with vancomycin.[8] Colorectal FMT, the most common FMT delivery method in Australia,[11] has been demonstrated to be similarly effective,[9, 10] without the risks of vomiting and aspiration associated with nasoduodenal delivery. The findings from the trials are consistent with observational evidence demonstrating the efficacy of FMT for treatment of recurrent CDI, which found treatment success rates for recurrent CDI ranging from 73% to 100%.[12]

This cost effectiveness analysis explores the economic and health outcomes of establishing FMT as the primary treatment for recurrent CDI in the Australian setting, enabling healthcare decision makers to determine the value of using FMT rather than standard vancomycin therapy, for the treatment of recurrent CDI.

METHODS

Model

A Markov model (see Fig. 1) was developed in TreeAge[5] to estimate the long-term costs and health outcomes of using either 1) standard vancomycin therapy, 2) nasoduodenal FMT, or 3) colorectal FMT for the treatment of recurrent CDI in Australia.

A cohort (N=1000) of patients was simulated in the Markov model beginning at the recurrent CDI health state. These patients were males and females, aged 65 years, who had a relapse of CDI after at least one course of antibiotic therapy (i.e., recurrent CDI). The Markov model had a cycle length of 10 days.

Successfully treated recurrent CDI patients moved into the “cure without relapse” health state. Recurrent CDI patients who do not respond to therapy can receive another round of treatment, require colectomy, die from fulminant colitis, or die from other causes. After one cycle in the "colectomy” state the patients moved to either the “dead” or “ileostomy” states. A proportion of the patients with ileostomy are eligible for ileostomy reversal. The model assumes that patients with ileostomy and those with reversed ileostomy are cured of CDI but are still subject to death from other causes.

Patients in the vancomycin treatment arm received 125 mg four times a day for 14 days for the first round of therapy and the same dose for 10 days in subsequent rounds of treatment.[13] The FMT arms received an abbreviated vancomycin regimen (125 mg orally 4 times per day for 4 to 5 days), followed by bowel lavage with macrogol solution prior to the delivery—nasoduodenal or colorectal—of FMT. If recurrent CDI developed after the first FMT treatment than the recurrent CDI patients received a second FMT treatment. Patients with subsequent CDI recurrences for either the vancomycin or FMT treatment arms were assumed to be treated with vancomycin. Each recurrence was assumed to result in an average increase of hospital stay of 3.6 days,[14] after which the patients receiving vancomycin continue their treatment regime after discharge.

Patients who have been cured of CDI are assumed to have the same baseline risk of developing CDI again as the general population. A patient in this model who becomes reinfected in this way re-enters the model. Patients in the model who are cured of recurrent CDI but then become reinfected received 400 mg metronidazole three times daily for 10 days. Reinfected CDI patients who progress to recurrent CDI received either FMT or vancomycin treatment according to their assigned treatment arm.

Economic costs were measured in 2015 Australian dollars (AU$) and health outcomes were measured in life years gained and quality adjusted life years (QALYs). Future costs and health outcomes were discounted at a rate of 5% in line with Australian standards.[20] Indirect costs incurred by the patient such as productivity loss and loss of leisure time are not measured directly in the model but are assumed to be captured by the QALY measure.[21]

Data sources

The data used to parameterise the model were identified from the literature (see Tables 1 and 2). The baseline probability of cure without relapse for patients with recurrent CDI and the treatment effect of FMT were based on clinical trial results.[8-10] The effectiveness of FMT is assumed to be the same regardless of mode of delivery. This is consistent with the results of a small pilot study that found nasoduodenal delivery to be as effective as colorectal administration.[10] Transition probabilities and

utility weights were based on those used in other economic models for CDI,[22-24] and epidemiological literature.[25] The background mortality rate is based on life tables published by the Australian Bureau of Statistics.[26]

Unit costs were taken from national databases and market prices.[27-30] The Pharmaceutical Benefits Schedule (PBS) provided costs for pharmaceuticals.[27] Costs for hospital stay, colectomy and ileostomy came from the National Hospital Cost Data Collection.[31] Hourly wages were based on Queensland Health wage rates.[32]

The cost of FMT in this model includes the costs associated with pre-treatment for the patient, obtaining, storing and preparing the faecal sample, and administering the faecal infusion. Pre-treatment costs include a 30-minute consultation with a gastroenterologist and pre-treatment with abbreviated vancomycin regimen. Pre-treatment for colonoscopy requires loperamide for FMT retention and bowel lavage. Costs of obtaining the faecal sample include advertising (2 hours of staff time to distribute flyers; AU$87) and a gratuity to the donors (AU$25). Preparation was assumed to require 2 hours of lab technologist time per treatment (AU$87). A specialist blender (AU$1,000) and freezer (AU$9,000) is required for the preparation and storage of the FMT sample,[15, 16] both are assumed to have a functional lifetime of 10 years and be used for 10 samples every year. Donor samples undergo serology (Hepatitis A, B and C; HIV, Syphilis, Strongyloides, ***Entamoeba histolytica***, Human T-lymphotropic virus) and faecal tests (microscopy, culture and sensitivities; ova, cysts and parasites; ***C. difficile***; rotavirus, norovirus and adenovirus).[12, 17-19] Administering the faecal infusion requires a radiologist and a gastroenterologist to place the nasoduodenal or colonoscopic tube and after the gastroenterologist has verified the placement of the tube in the duodenum a nurse, intern, or medical officer can administer the FMT sample. Cost of tube insertion was estimated based on similar Medicare Benefits Schedule (MBS) codes (MBS 32090 for colorectal FMT and 31458 for nasoduodenal FMT). Three hours of nursing supervision is assumed to be required after the procedure.

Analysis

The incremental costs and effectiveness were estimated for FMT and vancomycin and these values were used to calculate the incremental cost effectiveness ratio (ICER). Uncertainty around input parameters was explored through probabilistic sensitivity analysis using the Monte Carlo method with 1000 simulations. For parameters where standard error was not reported in the literature, values were imputed based on the researchers' estimate of reasonable variation.

RESULTS

Both nasoduodenal and colorectal FMT resulted in improved quality of life and reduced cost compared with vancomycin (Figs. 2 and 3). The incremental effectiveness of either FMT delivery compared with vancomycin was 1.2 (95% CI: 0.1, 2.3) QALYs, or 1.4 (95% CI: 0.4, 2.4) life years saved. Treatment with vancomycin resulted in an increased cost of AU$4,094 (95% CI: AU$26, AU$8,161) compared with nasoduodenal FMT and AU$4,045 (95% CI: -AU$33, AU$8,124) compared with colorectal FMT. The cost reduction due to FMT was largely a result of the faster recovery time reducing length of stay. The mean difference in cost between colorectal and nasoduodenal FMT was not significant (AU$48; 95% CI: -AU$1,177, AU$1,273).

Assuming an annual CDI incidence of 5,000 cases[5, 33, 34] and a recurrence rate of 6.8%,[24] the expected national cost savings of substituting FMT for vancomycin for the treatment of recurrent CDI would be over AU$1,370,000 per year.

DISCUSSION

If FMT, rather than vancomycin, became standard care for recurrent CDI in Australia, the estimated national healthcare savings would be over AU$4,000 per treated person, with a substantial increase in the quality of life. FMT is associated with higher upfront costs compared with vancomycin, but this upfront cost is more than compensated for by the increased effectiveness. This effectiveness—as demonstrated in both randomised controlled trial and observational evidence—results in reduced hospital stay and fewer adverse events leading to the identified cost savings and quality of life improvement.

The difference in cost between nasoduodenal and colorectal delivery is small and not significant given other sources of uncertainty. Moreover, the model did not incorporate the risks of nasogastric FMT over colorectal FMT such as aspiration and vomiting.

There is no direct evidence that the greater efficacy of FMT compared with vancomycin in treating recurrent CDI has an effect on mortality or the risk of colectomy. These long-term consequences were extrapolated from the original randomised controlled trial efficacy data using observational evidence. The model also assumes a constant efficacy rate for vancomycin after each round of treatment, however this assumption should be conservative, as the effectiveness of vancomycin would taper off after the first rounds of treatment.[8]

Making FMT cheaper will further increase the cost savings compared with vancomycin. Stool banks could reduce the cost of delivering FMT by allowing a single donor to provide multiple samples each of which can be used for the delivery of multiple FMTs.[18, 35, 36] There is an upfront cost in establishing a stool bank in terms of equipment, but with a large enough demand for FMT this would be overcome by the cost savings from reduced screening requirements. Omitting pre-treatment with vancomycin might also reduce the cost of FMT.

The costs of hospitalisation and adverse events in the model were based on public hospital costs. These costs are likely to be higher for private hospitals, and accordingly the cost savings associated with FMT are also likely to be higher for private hospitals.

FMT is often not available as a treatment option in Australian hospitals.[11] How FMT should be regulated remains contentious—particularly whether the faeces should be considered a therapeutic "drug", a biologic product or tissue.[18, 37] Patients have stated that they would be willing to receive FMT for recurrent CDI if it is recommended by their treating physician.[38-40] Given this willingness and the other benefits of FMT compared with antibiotic therapy, the inclusion of FMT as standard care for recurrent CDI is justified.

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Table 1 Cost components of FMT

Group	Item	Cost	Info Source
Non Consumable Equipment	Minus 80 degree freezer [1]	Cost of equipment $9,000 Cost per sample $160	Correspondence
	Specialist blender**Error! Bookmark not defined.**	Cost of equipment $1,000 Cost per sample $20	Correspondence
Staffing			
Pre-treatment work up	30min with gastroenterologist	$32 [2]	QLD payscales
Procedure itself	30-45min with gastroenterologist	$48**Error! Bookmark not defined.**	QLD payscales
Recovery time	2hrs of nursing time	$81	QLD payscales
Medical Procedures			

Testing patient prior to FMT	Patient screening	$119	Konijeti et al (2014)
Pre-treatment drug therapy	Abbreviated vancomycin regimen	$440	PBS
Testing donor prior to FMT	Donated material screening	$614 [3]	Correspondence
FMT preparation	2hrs of lab tech time per treatment	$87	QLD payscales
Instillation			
Colorectal delivery	Colonoscopy	$334	MBS 32090
	Loperamide for FMT retention (2x 2mg capsules)	$12	PBS

Table 2 Parameter inputs

Description (units)	Mean	SD	Distribution type	Source
Cost (AU$) FMT				
Colorectal	$2,251	$338*		Table 1
Nasoduodenal	$2,190	$315*		Table 1
Cost (AU$) vancomycin				
1st cycle: 125 mg four times a day, 14 days	$658	$99*	Gamma	PBS
Subsequent cycles: 125 mg four time a day, 10 days	$438	$66*	Gamma	PBS

Description (units)	Mean	SD	Distribution type	Source
Cost (AU$) metronidazole				
400 mg three times daily, 10 days	$27	$4*	Gamma	PBS
Cost (AU$) hospitalisation associated with recurrence				
Mean 3.6 days hospitalisation[14]	$4,467	$670*	Gamma	NHCDC†
Cost (AU$) Colectomy	$11,600	$1,740*	Gamma	NHCDC‡
Cost (AU$) ileostomy closure	$15,165	$2,275*	Gamma	NHCDC§
Utilities (QALY)				
uNat65 (age weight)	0.84	0.21*	Beta	[22]
uCDI	0.88	0.22*	Beta	[22]
uColectomy	0.536	0.13*	Beta	[22]
uIleostomy	0.7	0.18*	Beta	[22]
Transition probabilities (%), 10 day cycles				
tpCure (probability of cure without relapse)	0.308	0.05*	Log-Normal	[8]
tpCDImortality (mortality from CDI)	0.092	0.031*	Beta	[22]

Description (units)	Mean	SD	Distribution type	Source
tpColectomy (colectomy given CDI)	0.012	0.0251	Beta	[23]
tpCol_Mortality (post-colectomy mortality)	0.416	0.076	Beta	[22, 24]
tpReversal (ileostomy closure)	0.0005	0.0002*	Beta	[25]
tpCDIreinfection (reinfection with CDI)	0.0027	0.0011	Beta	[22]
tpCDIrecurrence (given reinfection)	0.1	0.04	Beta	[22]
Treatment effect (RR) FMT (nasoduodenal/colorectal)	3.05	0.47	Log Normal	[8]
Annual discount rate (%)				
Outcomes	5	NA	NA	[20]
Costs	5	NA	NA	[20]

AR-DRG, Australian Refined Diagnosis Related Groups; FMT, faecal microbiota transfusion; NA, not applicable; NHCDC, National Hospital Cost Data Collection; QALY, quality-adjusted life year; RR, relative risk; SD, standard deviation

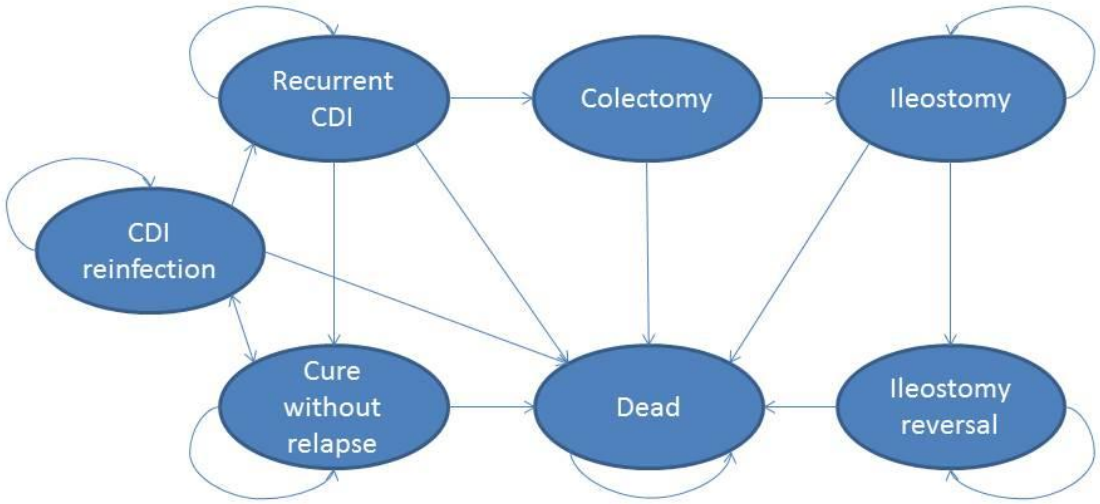

Figure 1 Structure of the Markov model

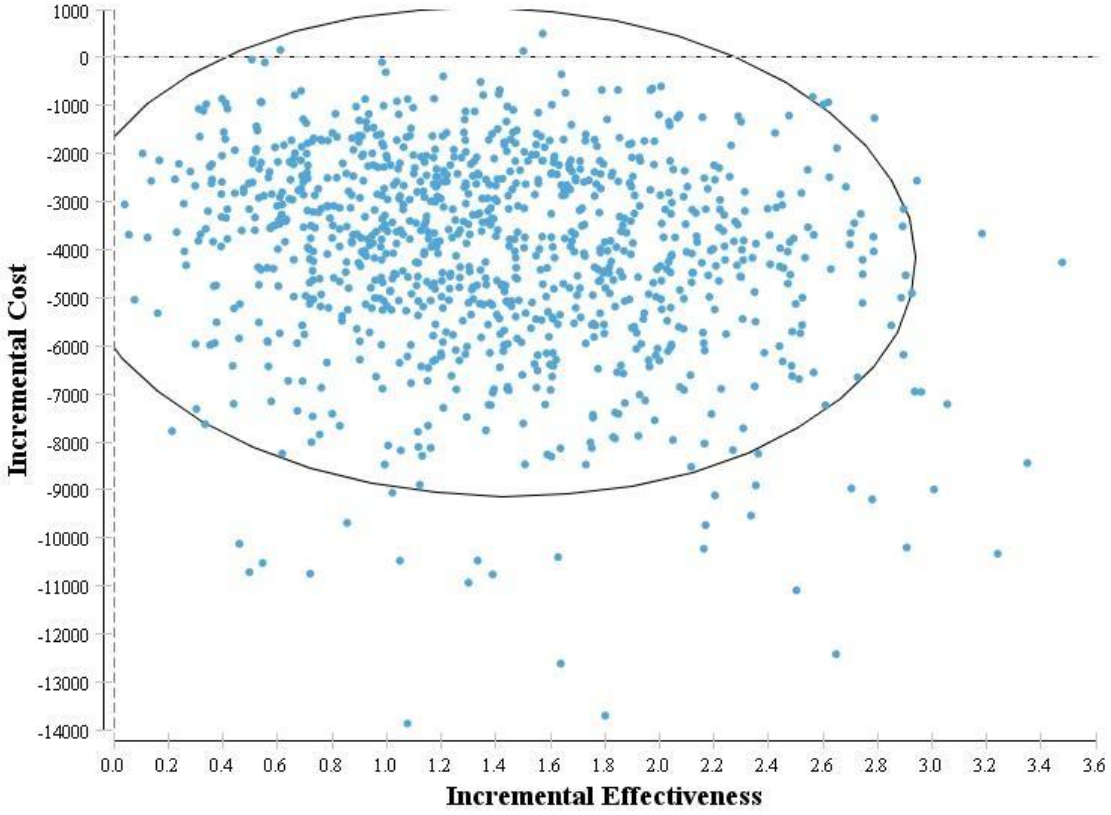

Figure 2: Scatterplot of the incremental cost-effectiveness of nasoduodenal FMT compared with vancomycin

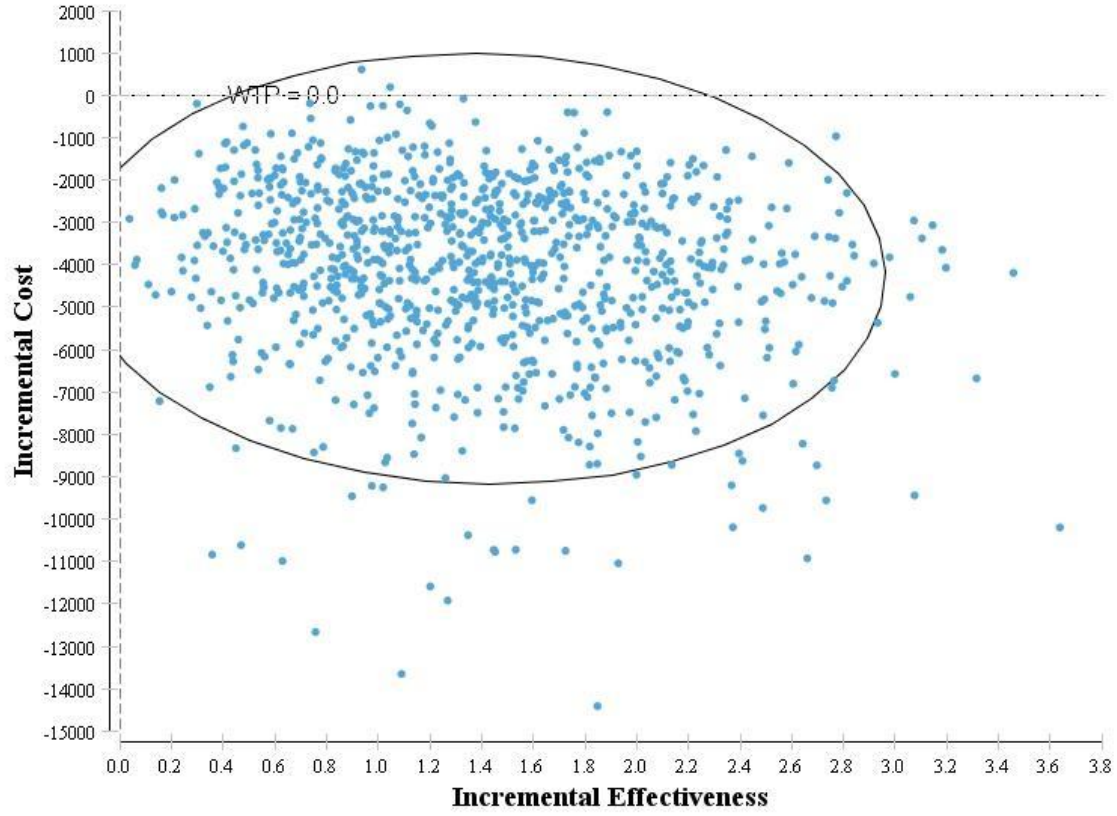

Figure 3: Scatterplot of the incremental cost-effectiveness of colorectal FMT compared with vancomycin

* Represents the authors' estimate of reasonable variation of these parameters.

† AR-DRG T64C: "Other Infectious and Parasitic Diseases without Catastrophic or Severe Complications or Comorbidities"

‡ AR-DRG G48A: "Colonoscopy with Catastrophic or Severe Complications or Comorbidities"

§ AR-DRG G02B: "Major Small and Large Bowel Procedures without Catastrophic Complications or Comorbidities"