

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Specification and Emulation of a Target Trial of Long-Acting Glycopeptides vs Standard of Care in Patients With Serious Bacterial Infections

Component	Target trial	Emulated trial using real-world data
Design	Multicentre open-label two-parallel arm superiority randomised trial.	
Aim	Estimate the effect of receiving long acting glycopeptides compared to standard of care in participants diagnosed with a serious bacterial infection on post-discharge outcomes	Same
Eligibility	1) 18 year or older;	Same
	2) Serious bacterial infections defined as a diagnosis of endocarditis, BSI, osteomyelitis, or septic arthritis;	Same
	3) Hospitalized	Diagnosis associated to a emergency room or hospitalization
	4) Gram-positive organism causing infection;	4) Received at least 7 days of gram-positive antibacterial coverage or long acting glycopeptide (dalbavancin or oritavancin) ¹
	5) Expected to survive until discharge	5) Survived until discharge
		6) Time of diagnosis between 1 October 2015 and 1 October 2022 ²
Exclusions	1) had a concomitant central nervous system infection;	Same
	2) endocarditis requiring early surgical intervention (less than 10 days from initial diagnosis date);	Same
	3) presence of a prosthetic heart valve;	Same
	4) presence of a cardiac device (implantable cardiac defibrillator, pacemaker);	Same
	5) presence of a transplanted organ (kidney, heart, lung, liver, pancreas, bone marrow);	Same
	6) end-stage renal disease or dialysis;	Same
	7) end-stage liver disease;	Same
	8) polymicrobial gram positive/gram negative infection	8) received end of therapy antibiotics not typical for gram positive organisms (e.g., broad spectrum antibiotic that cover gram negative organisms)
	9) received laLGP prior to enrolment	9) received laLGP prior to discharge day
Treatment strategies	1. Long acting glycopeptide (dalbavancin or oritavancin) 2. Standard of care antibiotics	Same

Treatment assignment	Patients are randomly assigned to either strategy once clinically stable.	Patients are non-randomly assigned to a treatment strategy. Randomisation is emulated via cloning of patients in both arms.
Treatment implementation	None	10 day grace period from discharge
Primary outcome	At 90 days post-discharge, composite outcome of: 1) Readmission, 2) Emergency room visit, 3) Death or hospice discharge	Same
Type of outcome	Composite; time to event	Same
Follow up	Follow up starts at discharge	Follow-up starts at discharge
Censoring	Loss to follow up, administrative censoring	Loss to follow up, administrative censoring, artificial censoring
Stratums	1) Persons who use drugs (PWUD) 2) Persons who do not use drugs	Same
Adjustment variables (all at baseline prior to exposure)		1) Age at diagnosis; 2) sex; 3) race; 4) ethnicity; 5) insurance coverage; 6) individual Elixhauser comorbidities; 7) facility location by 1-digit U.S. zip code, 8) facility bed size. For PWUD stratum, additionally: 1) History of methamphetamine, opioid, or cocaine use or disorder 2) Medications for opioid use disorder
Causal contrast	<i>Intention to treat and Per protocol analysis</i>	<i>Per protocol:</i> we do not know what the intention to treat was from the data; In each arm of the emulated trial, patients who deviate from the protocol are censored at their time of deviation
Estimands	Differences in 90-day outcomes 90-day survival and restricted mean survival time at 90 days between arms	Same
Notes:		

¹ Cerner Real World data did not contain culture data. Discharge antibiotics used in lieu to determine type of organism treated.

² Time period when long-acting glycopeptides were available in the United States.

eTable 2. Inclusion Criteria Diagnostic Codes

Variable name	ICD-10		ICD-9	
	Code	Diagnosis	Code	Diagnosis
Endocarditis	I33.X	Acute and subacute infective endocarditis	421.0	Acute and subacute bacterial endocarditis
	I38	Endocarditis, valve unspecified	421.1	Acute and subacute infective endocarditis in diseases classified elsewhere
	I39	Endocarditis and heart valve disorders in diseases classified elsewhere	421.9	Acute endocarditis, unspecified
			424.90	Endocarditis, valve unspecified, unspecified cause
			424.91	Endocarditis in diseases classified elsewhere
			424.99	Other endocarditis, valve unspecified
Bacteremia	R78.81	Bacteremia NOS	790.7	Bacteremia
Septic arthritis	M00.X	Pyogenic arthritis	711.0X	Pyogenic arthritis
			711.4X	Arthropathy associated with other bacterial diseases
			711.9X	Unspecified infective arthritis
Osteomyelitis	M86.X	Osteomyelitis	730.0X	Acute osteomyelitis
	M46.2	Osteomyelitis of vertebra	730.1X	Chronic osteomyelitis
	M46.21	Osteomyelitis of vertebra, occipito-atlanto-axial region	730.2X	Unspecified osteomyelitis
	M46.22	Osteomyelitis of vertebra, cervical region	730.8X	Other infections involving bone in diseases classified elsewhere
	M46.3	Infection of intervertebral disc (pyogenic)	730.9X	Unspecified infection of bone

eTable 3. Exclusion Diagnostic Codes

Variable name	ICD-10		ICD-9		Time frame
	Code	Diagnosis	Code	Diagnosis	
Other types of endocarditis	A32.82 A39.52 A54.83 B33.21 B37.6 I01.1 M32.11 A52.06	Listerial Meningococcal Gonococcal heart infection Viral Candidal Acute rheumatic Endocarditis in systemic lupus erythematosus Symptomatic cardiovascular syphilis	036.42 074.22 093.2x 098.84 112.81 115.04 115.14 115.94	Meningococcal Coxsackie carditis (viral) Syphilitic endocarditis Gonococcal Candidal Infection by Histoplasma capsulatum Infection by Histoplasma duboisii Histoplasmosis, unspecified,	Concurrent (+/- 15 days from inclusion diagnosis)
Central nervous system infections	A39.51 G06.X G00.X G01 B37.5	Meningococcal encephalitis Intracranial and intraspinal abscess and granuloma Bacterial meningitis, not elsewhere classified Meningitis in bacterial diseases classified elsewhere Fungal Meningitis	320.X 324.X	Bacterial meningitis Intracranial and intraspinal abscess	Concurrent (+/- 15 days from inclusion diagnosis)
End stage renal disease	N18.6 N18.5	End stage renal disease Chronic kidney disease, stage 5	585.6 585.5	End stage renal disease Chron kidney dis stage V	Prior (anytime before inclusion diagnosis)
End stage liver disease	K72.1X K74.X K70.2 K70.3	Chronic hepatic failure Fibrosis and cirrhosis of liver Alcoholic fibrosis and sclerosis of liver	572.8 571.5 571.2	Other sequelae of chronic liver disease Cirrhosis of liver without mention of alcohol	Prior (anytime before inclusion diagnosis)

Variable name	ICD-10		ICD-9		Time frame
	Code	Diagnosis	Code	Diagnosis	
	K70.4	Alcoholic cirrhosis of liver Alcoholic hepatic failure		Alcoholic cirrhosis of liver	
Prosthetic valves	Z95.2	Presence of a Prosthetic Heart Valve	V43.3	Heart valve replaced by other means	Prior (anytime before inclusion diagnosis)
	Z95.3	Presence of xenogenic heart valve	V42.2	Heart valve replaced by transplant	
	Z95.4	Presence of other heart-valve replacement	996.02	Mechanical complication due to heart valve prosthesis	
	T82.0	Mechanical complication of heart valve prosthesis	996.61	Infection and inflammatory reaction due to cardiac device, implant, and graft	
	T82.6	Infection and inflammatory reaction due to cardiac valve prosthesis			
Other cardiac devices (ICD, pacemaker)	Z95.0	Presence of cardiac pacemaker	V45.0	Cardiac device in situ	Prior (anytime before inclusion diagnosis)
	Z95.81	Presence of other cardiac implants and grafts	996.01	Mechanical complication due to cardiac pacemaker (electrode)	
	T82.1	Mechanical complication of cardiac electronic device	996.04	Mechanical complication of automatic implantable cardiac defibrillator	
Transplant	Z94.0	Kidney transplant status	V42.0	Kidney replaced by transplant	Prior (anytime before inclusion diagnosis)
	Z94.1	Heart transplant status	V42.1	Heart replaced by transplant	
	Z94.2	Lung transplant status	V42.2	Heart valve replaced by transplant	
	Z94.3	Heart and lungs transplant status		Lung replaced by transplant	
	Z94.4		V42.6	Lung replaced by transplant	

Variable name	ICD-10		ICD-9		Time frame
	Code	Diagnosis	Code	Diagnosis	
	Z94.8	Liver transplant status	V42.7	Liver replaced by transplant	
		Other transplanted organ and tissue status	V42.8	Other specified organ or tissue replaced by transplant	
	Z94.81	Bone marrow transplant status		Bone marrow replaced by transplant	
	Z94.83	Pancreas transplant status	V42.81	Pancreas replaced by transplant	
	Z94.84	Stem cells transplant status	V42.82	Peripheral stem cells replaced by transplant	
	T86X	Complications of transplanted organs and tissue	V42.83	Pancreas replaced by transplant	
	Z48.2	Encounter for aftercare following organ transplant	996.8	Complications of transplanted organ	
			V58.44	Aftercare following organ transplant	

eTable 4. Exclusion Procedure Codes

Associated Procedure(s)	CPT Code(s)	ICD-10-PCS Code(s)	ICD-9 Procedure Code(s)	Time frame
End Stage Renal Disease				
Hemodialysis	36558 36800 36810 36815 Insertion of cannula for hemodialysis 90935 90937 Hemodialysis	5A1D Urinary ultrafiltration 02H633Z 02HV33Z 0JH63XZ Insertion of catheter	39.95 Hemodialysis	Prior (anytime before inclusion diagnosis)
Peritoneal dialysis	90945 90947 Dialysis other than hemodialysis 49324 49481 49421 Insertion peritoneal catheter	3E1M39Z 0WHG03Z 0WHG33Z 0WHG43Z Insertion infusion device in peritoneal cavity	54.98 Peritoneal dialysis	Prior (anytime before inclusion diagnosis)
Arteriovenous fistula - graft creation	36818 36819 36820 36821 36825 36830 36832 36833 36838 Arteriovenous anastomosis	031T0ZZ 031V0DZ	39.27 Arteriovenostomy for renal dialysis 39.42 Revision of arteriovenous shunt for renal dialysis 39.43 Removal of arteriovenous shunt for renal dialysis	Prior (anytime before inclusion diagnosis)
Transplant				
Kidney	50300 50320 50323 50325	0TY00Z0 0TY00Z1 0TY00Z2 0TY10Z0 0TY10Z1 0TY10Z2 0TYK0Z0 0TYK0Z1	55.6 Kidney transplantation	Prior (anytime before

Associated Procedure(s)	CPT Code(s)	ICD-10-PCS Code(s)	ICD-9 Procedure Code(s)	Time frame
	50327 50328 50329 50340 50360 50365 50370 50380 S2065	0TYL0Z0 0TYL0Z1 (combined kidney and pancreas)	55.61 Transplant from live related donor 55.69 Kidney transplant NEC	inclusion diagnosis)
Pancreas	48160 48550 48551 48552 48554 48556 S2065 S2102 0584T 0585T 0586T	0FYG0Z0 0FYG0Z1 0FYG0Z2	52.8 Transplant Of Pancreas	Prior (anytime before inclusion diagnosis)
Liver	47133 47135 47140 47141 47142 47143 47144 47145 47146 47147 47399 S2152	0FY00Z0 0FY00Z1 0FY00Z2	50.5 Liver Transplant	Prior (anytime before inclusion diagnosis)
Heart	33927 33928 33929 33930 33933 33935 33940 33944 33945 S2152	02YA0Z0 02YA0Z1 02YA0Z2 02RK0JZ 02RL0JZ	37.51 Heart Transplantation	Prior (anytime before inclusion diagnosis)
Lung	32850 32851	0BYC0Z0 0BYC0Z1 0BYC0Z2 0BYD0Z0	33.5 Lung Transplant	Prior (anytime

Associated Procedure(s)	CPT Code(s)	ICD-10-PCS Code(s)	ICD-9 Procedure Code(s)	Time frame
	32852 32853 32854 32855 32856 S2060 S2061	0BYD0Z1 0BYD0Z2 0BYF0Z0 0BYF0Z1 0BYF0Z2 0BYG0Z0 0BYG0Z1 0BYG0Z2 0BYH0Z0 0BYH0Z1 0BYH0Z2 0BYJ0Z0 0BYJ0Z1 0BYJ0Z2 0BYK0Z0 0BYK0Z1 0BYK0Z2 0BYL0Z0 0BYL0Z1 0BYL0Z2 0BYM0Z0 0BYM0Z1 0BYM0Z2	33.6 Combined heart-lung transplantation	before inclusion diagnosis)
Intestine	44132 44133 44135 44136 44137	0DY60Z0 0DY60Z1 0DY80Z0 0DY80Z1 0DY80Z2 0DYE0Z0 0DYE0Z1 0DYE0Z2 0DYF0Z0 0DYF0Z1	46.97: Intestinal transplant 46.98: Combined liver-intestine transplant	Prior (anytime before inclusion diagnosis)
Bone marrow	38205-38215 38231-38231 38240-38243 86915-86915 G0267-G0267 S2140-S2140	XW033C3 XW043C3 30230AZ 30230G0 30230Y0 30233AZ 30233G0 30233Y0 30243AZ 30243G0 30243Y0 30253G0 30253Y0 30263G0 30263Y0 30240AZ 30240G0 30240Y0 30250G0 30250Y0 30260G0 30260Y0 30230G2 30230G3 30230G4 30230X0 30230X2 30230X3 30230X4 30230Y2 30230Y3 30230Y4 30233G2 30233G3 30233G4 30233X2 30233X3 30233X4 30233Y2 30233Y3 30233Y4 30240G2 30240G3 30240G4 30240X0 30240X2 30240X3 30240X4 30240Y2 30240Y3 30240Y4 30243G2	41.0 Bone Marrow or Hematopoietic Stem Cell Transplant	Prior (anytime before inclusion diagnosis)

Associated Procedure(s)	CPT Code(s)	ICD-10-PCS Code(s)	ICD-9 Procedure Code(s)	Time frame
		30243G3 30243G4 30243X2 30243X3 30243X4 30243Y2 30243Y3 30243Y4 30250G1 30250X0 30250X1 30250Y1 30260G1 30260X0 30260X1 30260Y1 30233X0 30243X0 30253G1 30253X0 30253X1 30253Y1 30263G1 30263X0 30263X1 30263Y1		
Cardiac related				
Pacemaker /Implantable cardiac defibrillator	33206 33207 33208 33202 33203 33215 33216 33217 33218 33220 33223 33224 33225 33230 33231 33240 33241 33243 33244 33249 33262 33263 33264 33270 33271 33272 33273 C7537 C7538 C7539	02HK0KZ 02HK3KZ 02HK4KZ 02HL0KZ 02HL3KZ 02HL4KZ 02HL0MZ 02HL3MZ 02HL4MZ 02H60KZ 02H63KZ 02H64KZ 02H70KZ 02H73KZ 02H74KZ 0JH60AZ 0JH63AZ 0JH80AZ 0JH83AZ 0JH606Z 0JH636Z 0JH607Z 0JH637Z 0JH608Z 0JH638Z 0JH60GZ 0JH63GZ 0JH60JZ 0JH63JZ 0JH60PZ 0JH63PZ 0JH60QZ 0JH63QZ 0JH60KZ 0JH63KZ 0JPT0ZZ 0JPT3ZZ 0JPT4ZZ 0JH60LZ 0JH63LZ 0JH60MZ 0JH63MZ 0JH60NZ 0JH63NZ	37.52 Implantation of total internal biventricular heart replacement system 37.8X Insertion, Replacement, Removal And Revision Of Pacemaker Device	Prior (anytime before inclusion diagnosis)

eTable 5. Codes to Identify People Who Use Drugs

Diagnosis category	ICD-9	ICD-10	SNOMED CT
Opioid related codes	965.00 965.01 965.02 965.09 970.1 304.0X 304.7X 305.5X E850.0 E850.1 E850.2 E940.1	T40.0 T40.1 T40.2 T40.3 T40.4 F11X	297199006 11196001 74264003 216469009 295174006 295175007 295176008 242829007 13187008 216463005 290183003 290182008 47836003 60199004 68099003 216464004 216466002 216468001 241749009 242253008 242828004 242831003 290171000 290172007 290174008 290175009 290176005 290177001 290179003 290180000 290193005 290194004 290201006 290202004 290203009 290204003 295161000 295163002 295164008 295166005 295167001 295168006 295169003 295170002 295171003 295172005 295173000 295184007 295185008 295186009 295187000 295193008 295194002 295195001 295196000 295213004 297199006 231477003 75544000 191865004 191820008 426001001 231478008 231479000 231480002 77721001 5602001 191909007 191819002 145121000119106 191912005 191913000
Cocaine related codes	970.81 304.2X 305.6X E938.5	T40.5 F14X	296321004 296324007 296322006 296323001 296325008 296326009 296327000 296328005 31956009 191831000 191832007 27956007 78267003 145101000119102 191916008 191918009 191919001 428493006
Methamphetamine related codes	969.70 969.71 969.72 969.73 969.79 304.4X 305.7X	T43.6 F15X	20260003 21647008 45775001 61803000 212670004 216558009 216559001 242257009 291241005 291242003 291258000 291259008 291260003 296290006 296291005 296292003 296293008 296294002 296317006 296318001 296329002 426873000 275471001 21647008 191843004 191844005 191877009 45421006 84758004 191924003 191925002 268648009 275471001 427205009 428659002 429692000 699449003

Database	Terms/Codes	Descriptors
SNOMED	75544000	Opioid dependence
	699449003	Methamphetamine abuse
	228388006	Intravenous drug user
	5602001	Opioid abuse
	371435006	History of drug abuse
	26416006	Drug abuse
	426873000	Methamphetamine dependence
	191819002	Continuous opioid dependence
	361055000	Misuses drugs
	724653003	Opioid dependence with current use
	16464661000119100	History of intravenous drug abuse
	78267003	Cocaine abuse
	231477003	Heroin dependence
	70545002	Narcotic drug user
	191816009	Drug dependence
	11061003	Psychoactive substance use disorder
	191909007	Nondependent opioid abuse
	1081000119105	Opioid dependence, on agonist therapy
	441527004	Stimulant abuse
	55680006	Drug overdose
	6525002	Dependent drug abuse
	27660001000004100	History of methamphetamine abuse
	307052004	Illicit drug use
	31956009	Cocaine dependence
	49540005	Non dependent drug abuse
	733461000	Cocaine user
	1471000119103	Drug abuse in remission
	191821007	Opioid dependence in remission
	191865004	Combined opioid with other drug dependence
	228373001	Drug addict
	442406005	Stimulant dependence
	169941005	Maternal drug abuse
	426001001	Fentanyl dependence
	741063003	Illicit drug injection in last 12 months
	12398571000119100	Methamphetamine intoxication
	191833002	Cocaine dependence in remission
	191934007	Nondependent mixed drug abuse
	231481003	Controlled drug dependence
	295174006	Heroin overdose
	387341002	Heroin
	428493006	Crack cocaine misuse
	59274003	Intentional drug overdose
	59369008	Accidental drug overdose
	110281001	Chronic drug abuse
	12398281000119100	Methamphetamine withdrawal

Database	Terms/Codes	Descriptors
	12398321000119100 13187008 14816004 153501000119105 191845006 191914006 191918009 191920007 191937000 191938005 229003004 231482005 237228001 288791000119106 288811000119105 288831000119100 288851000119106 292063009 295175007 310653000 34150001 373492002 424848002 425533007 428370001 429782000 762327001 8692006 295176008 295196000 371341003 295213004 297199006	Mood disorder caused by methamphetamine Poisoning by heroin Cocaine product Drug dependence, episodic Amphetamine or psychostimulant dependence in remission Nondependent opioid abuse in remission Nondependent cocaine abuse, continuous Nondependent cocaine abuse in remission Nondependent mixed drug abuse, episodic Nondependent mixed drug abuse in remission Cocaine freebase Active drug dependence Pregnancy and drug dependence History of cocaine abuse History of heroine abuse History of opioid abuse Opioid-induced mood disorder due to opioid abuse Fentanyl adverse reaction Accidental heroin overdose Drug addiction therapy - methadone Drug dependence in mother complicating pregnancy, childbirth AND/OR puerperium Fentanyl Recreational drug user Episodic drug abuse Psychostimulant withdrawal Cocaine misuse Psychotic disorder with delusions caused by stimulant Methamphetamine Heroin overdose of undetermined intent Fentanyl overdose of undetermined intent Drug overdose of undetermined intent Overdose of opiate analgesic of undetermined intent Accidental overdose of opiate
ICD-10	F11 F14 F15 T40.0 T40.1 T40.2 T40.3 T40.4	Opioid related disorders Cocaine related disorders Stimulant (methamphetamine) related disorders Poisoning by, adverse effect of and underdosing of opium Poisoning by and adverse effect of heroin Poisoning by, adverse effect of and underdosing of other opioids Poisoning by, adverse effect of and underdosing of methadone

Database	Terms/Codes	Descriptors
	T40.5 T40.6 T43.62 T43.64 T43.65 T43.66	Poisoning by, adverse effect of and underdosing of other synthetic narcotics Poisoning by, adverse effect of and underdosing of cocaine Poisoning by, adverse effect of and underdosing of other and unspecified narcotics Poisoning by, adverse effect of and underdosing of amphetamines Poisoning by ecstasy Poisoning by, adverse effect of and underdosing of methamphetamines Poisoning by, adverse effect of and underdosing of other psychostimulants
ICD-9	304.0X 304.7X 305.5X E854.2	Opioid type dependence Combinations of opioid type drug with any other drug dependence Opioid abuse Poisoning by opiates and related narcotics Poisoning by opiate antagonists Accidental poisoning by heroin Accidental poisoning by methadone Accidental poisoning by other opiates and related narcotics Adverse effects of opiate antagonists Accidental poisoning by psychostimulants Poisoning by psychostimulant, unspecified Poisoning by amphetamines Poisoning by other psychostimulants

eTable 6. Antibiotic Characteristics for PWUD Group

Variable	SOC, N = 4,806	laLGP, N = 241
Terminal antibiotics, n (%)		
Vancomycin	933 (19%)	
Cefazolin	848 (18%)	
Trimethoprim/sulfamethoxazole	572 (12%)	
Doxycycline	556 (12%)	
Cephalexin	554 (12%)	
Daptomycin	445 (9.3%)	
Linezolid	383 (8.0%)	
Nafcillin	210 (4.4%)	
Cefadroxil	30 (0.6%)	
Oxacillin	92 (1.9%)	
Ceftaroline	86 (1.8%)	
Days, terminal antibiotics, Median (IQR)	13 (6 – 30)	
Days, prior to laLGP, Median (IQR)		22 (12 – 41)
laLGP doses, Median (IQR)		2.00 (1.00 – 2.00)
Abbreviations: laLGP, long acting lipoglycopeptide; IQR, interquartile range; SOC, standard of care antibiotics. Antibiotics less than 1% were truncated from list.		

eTable 7. Antibiotic Characteristics for Non-PWUD Group

Variable	SOC, N = 36,436	laLGP, N = 584
Terminal antibiotics, n (%)		
Cefazolin	7,150 (20%)	
Vancomycin	6,702 (18%)	
Cephalexin	6,409 (18%)	
TMP/SMX	4,502 (12%)	
Doxycycline	4,251 (12%)	
Daptomycin	2,594 (7.1%)	
Linezolid	2,105 (5.8%)	
Nafcillin	963 (2.6%)	
Cefadroxil	476 (1.3%)	
Oxacillin	456 (1.3%)	
Ceftaroline	376 (1.0%)	
Days, terminal antibiotics, Median (IQR)	10 (5 – 27)	
Days, prior to laLGP, Median (IQR)		14 (7 – 32)
laLGP doses, Median (IQR)		2.00 (1.00 – 2.00)
Abbreviations: laLGP, long acting lipoglycopeptide; IQR, interquartile range; SOC, standard of care antibiotics. Antibiotics less than 1% were truncated from list.		