Progress And Pitfalls In Getting Clinicians The Trials That They Need

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Disclosures

Nature of Relevant Financial Relationship	Commercial Interest
Grant or research support	Cerexa/Actavis, Pfizer, Advanced Liquid Logics, NIH, MedImmune, Cubist/Merck; Karius; Contrafect; Genentech NIH STTR/SBIR grants pending: Affinergy; Locus, Medical Surface, Inc.
Paid consultant	Achaogen, Astellas, Arsanis; Affinergy; Basilea; Bayer; Cerexa, Contrafect; Cubist; Debiopharm, Durata, Grifols; Genentech; MedImmune, Merck, Medicines Co; Pfizer, Novartis, Novadigm, Theravance; xBiotech,
Speaker's Bureau	None
Employment	Duke University
Honoraria	Theravance; Green Cross
Membership on advisory committees or review panels, board membership,	Chair- Merck V710 Advisory Board Committee
Ownership Interest (e.g., stocks, stock options or other interests	NONE
Other relevant financial interests	Patent pending in sepsis diagnostic

Points of this Talk

- **Registrational Trials:** *Necessary, Not Sufficient*
- **Strategy Trials:** *Giving the people what they want*
- **Clinical Networks:** *Improve US Site Enrollment in both*

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MJA 2013; 198: 270–272

What Clinicians Want

Proposal Subject	Clinical Requests
Duration of IV antibiotics	5
Combination antibiotic therapy	3
Treatment of MDR Pathogens	3
Route of Administration	2

What Clinicians Get:

FDA-Approved Agents By Indication: 2013- 2018

Acute Bacterial Skin and Skin Structure Infection (ABSSSI)	4	Dalbavancin (2014) Oritavancin (2014) Tedizolid (2014) Delafloxacin (2018)
Complicated Urinary Tract Infection (cUTI)	4	Ceftolazone/tazobactam (2014) Ceftazadime/avibactam (2015) Meropenem/vaborbacam (2017) Plazomicin (2018)
Complicated Intraabdominal Infection (cIAI)	3	Ceftolazone/tazobactam (2014) Ceftazadime/avibactam (2015) Eravacycline (2018)
Hospital-Acquired Bacterial Pneumonia / Ventilator-Associated Bacterial Pneumonia (HABP/VABP)	1	Telavancin (2013)
Clostridium difficile	1	Bezlotoxumab (2016)

https://www.centerwatch.com/drug-information/fda-approved-drugs/

Phase 3 Trials in 2018

Complicated UTI

JAMA | Original Investigation

Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection

The TANGO I Randomized Clinical Trial

Keith S. Kaye, MD, MPH; Tanaya Bhowmick, MD; Symeon Metallidis, MD; Susan C. Bleasdale, MD; Olexiy S. Sagan, MD; Viktor Stus, MD, PhD; Jose Vazquez, MD; Valerii Zaitsev, PhD; Mohamed Bidair, MD; Erik Chorvat, MD; Petru Octavian Dragoescu, MD; Elena Fedosiuk, MD; Juan P. Horcajada, MD, PhD; Claudia Murta, MD; Yaroslav Sarychev, MD; Ventsislav Stoev, MD; Elizabeth Morgan, BS; Karen Fusaro, BS; David Griffith, BS; Olga Lomovskaya, PhD; Elizabeth L. Alexander, MD; Jeffery Loutit, MBChB; Michael N. Dudley, PharmD; Evangelos J. Giamarellos-Bourboulis, MD, PhD

JAMA. 2018;319(8):788-799.

...meropenem-vaborbactam vs piperacillin-tazobactam resulted in a composite outcome of complete resolution or improvement of symptoms along with microbial eradication that met the noninferiority criterion.

ABSSSI

J Antimicrob Chemother 2017; **72**: 3471–3480
doi:10.1093/jac/dkx329 Advance Access publication 5 October 2017

Journal of Antimicrobial Chemotherapy

Efficacy and safety of delafloxacin compared with vancomycin plus aztreonam for acute bacterial skin and skin structure infections: a Phase 3, double-blind, randomized study

J. Pullman[1], J. Gardovskis[2], B. Farley[3], E. Sun[4], M. Quintas[4], L. Lawrence[4], R. Ling[5] and S. Cammarata[4]* on behalf of the PROCEED Study Group†

A Comparison of the Efficacy and Safety of Intravenous Followed by Oral Delafloxacin With Vancomycin Plus Aztreonam for the Treatment of Acute Bacterial Skin and Skin Structure Infections: A Phase 3, Multinational, Double-Blind, Randomized Study

William O'Riordan,[1] Alison McManus,[1] Juri Teras,[2] Ivan Poromanski,[3] Maria Cruz-Saldariagga,[4] Megan Quintas,[5] Laura Lawrence,[5] ShuJui Liang,[6] and Sue Cammarata[5]; for the PROCEED Study Group[a]

[1]E-study Site, Chula Vista, California; [2]North Estonia Medical Centre Foundation, Tallinn; [3]Purulent-Septic Surgery Clinic, Multiprofile Hospital Active Treatment and Emergency Medicine, Pirogov EAD, Bulgaria; [4]Hospital Nacional Adolfo Guevara Velasco, Cusco, Peru; [5]Melinta Therapeutics, Lincolnshire, Illinois; and [6]H2O Clinical, Hunt Valley, Maryland

Clinical Infectious Diseases® 2018;67(5):657–66

ABSSSI

A Phase 3, Randomized, Double-Blind, Multicenter Study to Evaluate the Safety and Efficacy of Intravenous Iclaprim Vs Vancomycin for the Treatment of Acute Bacterial Skin and Skin Structure Infections Suspected or Confirmed to be Due to Gram-Positive Pathogens: REVIVE-1

David B. Huang,[1] William O'Riordan,[2] J. Scott Overcash,[2] Barry Heller,[3] Faisal Amin,[4] Thomas M. File,[5] Mark H. Wilcox,[6] Antoni Torres,[7] Matthew Dryden,[8] Thomas L. Holland,[9] Patrick McLeroth,[10] Rajesh Shukla,[1] and G. Ralph Corey[9]

Clinical Infectious Diseases® 2018;66(8):1222–9

A Phase 3, Randomized, Double-Blind, Multicenter Study To Evaluate the Safety and Efficacy of Intravenous Iclaprim versus Vancomycin for Treatment of Acute Bacterial Skin and Skin Structure Infections Suspected or Confirmed To Be Due to Gram-Positive Pathogens (REVIVE-2 Study)

Thomas L. Holland,[a] William O'Riordan,[b] Alison McManus,[b] Elliot Shin,[b] Ali Borghei,[c] Thomas M. File, Jr.,[d] Mark H. Wilcox,[e] Antoni Torres,[f,g] Matthew Dryden,[h] Thomas Lodise,[i] Toyoko Oguri,[j] G. Ralph Corey,[a] Patrick McLeroth,[j] Rajesh Shukla,[k] David B. Huang[k]

May 2018 Volume 62 Issue 5 e02580-17 Antimicrobial Agents and Chemotherapy

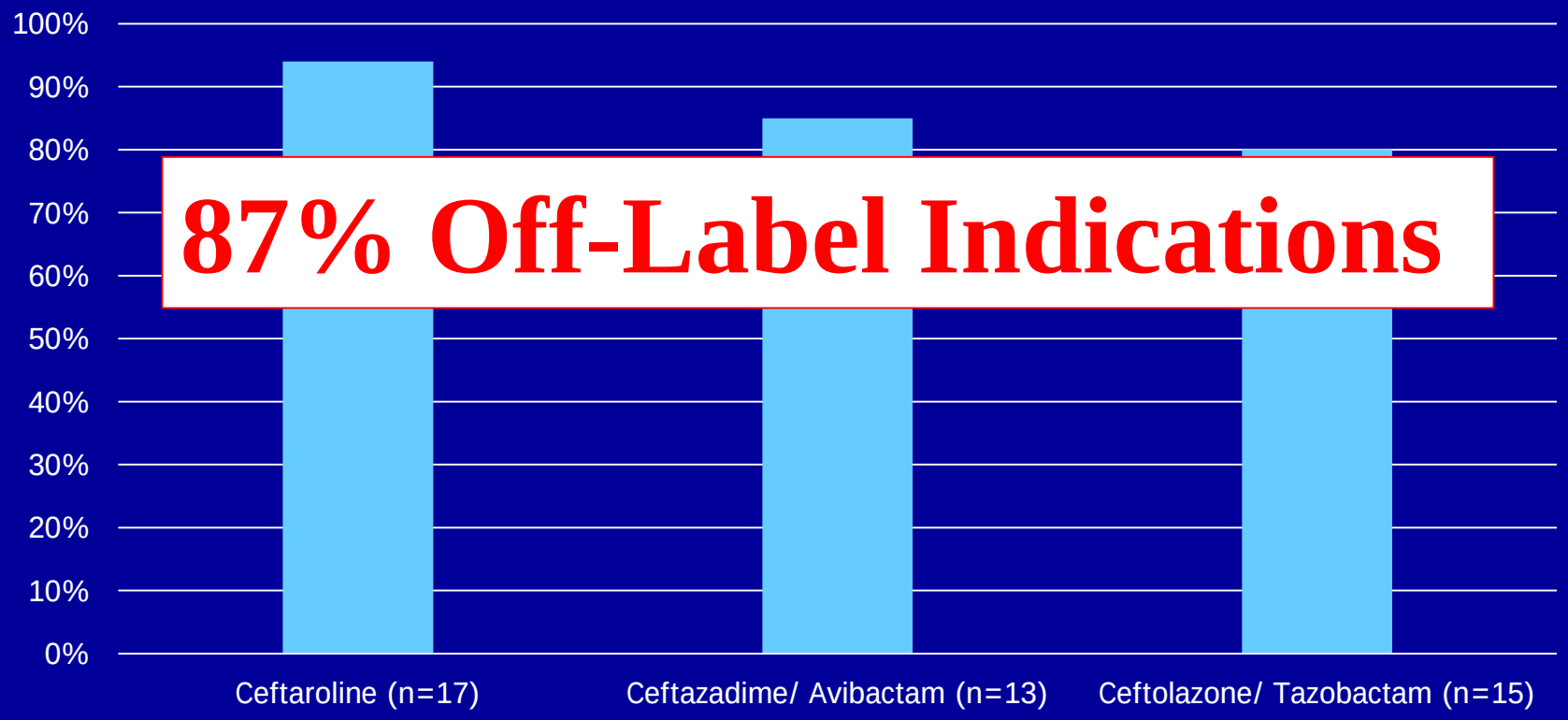
Proposal Subject	Clinical Requests	Addressed by Registrational Trials since 2013
Duration of IV antibiotics	5	0
Combination antibiotic therapy	3	0
Treatment of MDR Pathogens	3	0
Route of Administration	2	0

What Clinicians are Doing

Uses for 3 Newly Approved Antibiotics

Ceftaroline, Ceftazadime/Avibactam, Ceftolazone/ Tazobactam

May 1- August 1, 2018 Duke University Hospital



An Inconvenient Truth: Clinical Trials ≠ Clinical Practice

Erythema not receding in 72h ≠ failure.

Not obtaining a blood culture 6 weeks after stopping antibiotics ≠ failure.

4 days of Drug B after treatment with Drug A ≠ failure.

Points of this Talk

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Strategy Trials in 2018

JAMA | Original Investigation

Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women
A Randomized Clinical Trial

Angela Huttner, MD; Anna Kowalczyk, MS; Adi Turjeman, MSc; Tanya Babich, MSc; Caroline Brossier, RN; Noa Ellakim-Raz, MD; Katarzyna Kosiek, MD, PhD; Begoña Martinez de Tejada, MD, PhD; Xavier Roux, MD; Shachaf Shiber, MD; Ursula Theuretzbacher, PhD; Elodie von Dach, PhD; Dafna Yahav, MD; Leonard Leibovici, MD; Maciek Godycki-Ćwirko, MD, PhD; Johan W. Mouton, MD, PhD; Stephan Harbarth, MD

JAMA. 2018;319(17):1781-1789.

"Among women with uncomplicated UTI, 5-day nitrofurantoin, compared with single-dose fosfomycin, resulted in a significantly greater likelihood of clinical and microbiologic resolution at 28 days after therapy completion."

Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial

Mical Paul, George L Daikos, Emanuele Durante-Mangoni, Dafna Yahav, Yehuda Carmeli, Yael Dishon Benattar, Anna Skiada, Roberto Andini, Noa Eliakim-Raz, Amir Nutman, Oren Zusman, Anastasia Antoniadou, Pia Clara Pafundi, Amos Adler, Yaakov Dickstein, Ioannis Pavleas, Rosa Zampino, Vered Daitch, Roni Bitterman, Hiba Zayyad, Fidi Koppel, Inbar Levi, Tanya Babich, Lena E Friberg, Johan W Mouton, Ursula Theuretzbacher, Leonard Leibovici

Lancet Infect Dis 2018; 18: 391–400

"The addition of meropenem to colistin did not improve clinical failure in severe Acinetobacter baumannii infections."

ORIGINAL ARTICLE

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Kasper Iversen, M.D., D.M.Sc., Nikolaj Ihlemann, M.D., Ph.D., Sabine U. Gill, M.D., Ph.D., Trine Madsen, M.D., Ph.D., Hanne Elming, M.D., Ph.D., Kaare T. Jensen, M.D., Ph.D., Niels E. Bruun, M.D., D.M.Sc., Dan E. Høfsten, M.D., Ph.D., Kurt Fursted, M.D., D.M.Sc., Jens J. Christensen, M.D., D.M.Sc., Martin Schultz, M.D., Christine F. Klein, M.D., Emil L. Fosbøll, M.D., Ph.D., Flemming Rosenvinge, M.D., Henrik C. Schønheyder, M.D., D.M.Sc., Lars Køber, M.D., D.M.Sc., Christian Torp-Pedersen, M.D., D.M.Sc., Jannik Helweg-Larsen, M.D., D.M.Sc., Niels Tønder, M.D., D.M.Sc., Claus Moser, M.D., Ph.D., and Henning Bundgaard, M.D., D.M.Sc.

DOI: 10.1056/NEJMoa1808312

"In patients with endocarditis on the left side of the heart who were in stable condition, changing to oral antibiotic treatment was noninferior to continued intravenous antibiotic treatment."

Adjunctive rifampicin for *Staphylococcus aureus* bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial

*Guy E Thwaites, Matthew Scarborough, Alexander Szubert, Emmanuel Nsutebu, Robert Tilley, Julia Greig, Sarah A Wyllie, Peter Wilson, Cressida Auckland, Janet Cairns, Denise Ward, Pankaj Lal, Achyut Guleri, Neil Jenkins, Julian Sutton, Martin Wiselka, Gonzalez-Ruiz Armando, Clive Graham, Paul R Chadwick, Gavin Barlow, N Claire Gordon, Bernadette Young, Sarah Meisner, Paul McWhinney, David A Price, David Harvey, Deepa Nayar, Dakshika Jeyaratnam, Tim Planche, Jane Minton, Fleur Hudson, Susan Hopkins, John Williams, M Estee Török, Martin J Llewelyn, Jonathan D Edgeworth, A Sarah Walker, on behalf of the United Kingdom Clinical Infection Research Group (UKCIRG)**

Lancet 2018; 391: 668–78

"Adjunctive rifampicin provided no overall benefit over standard antibiotic therapy in adults with S aureus bacteraemia."

JAMA | Original Investigation

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance

A Randomized Clinical Trial

Patrick N. A. Harris, MBBS; Paul A. Tambyah, MD; David C. Lye, MBBS; Yin Mo, MBBS; Tau H. Lee, MBBS; Mesut Yilmaz, MD; Thamer H. Alenazi, MD; Yaseen Arabi, MD; Marco Falcone, MD; Matteo Bassetti, MD, PhD; Elda Righi, MD, PhD; Benjamin A. Rogers, MBBS, PhD; Souha Kanj, MD; Hasan Bhally, MBBS; Jon Iredell, MBBS, PhD; Marc Mendelson, MBBS, PhD; Tom H. Boyles, MD; David Looke, MBBS; Spiros Miyakis, MD, PhD; Genevieve Walls, MB, ChB; Mohammed Al Khamis, MD; Ahmed Zikri, PharmD; Amy Crowe, MBBS; Paul Ingram, MBBS; Nick Daneman, MD; Paul Griffin, MBBS; Eugene Athan, MBBS, MPH, PhD; Penelope Lorenc, RN; Peter Baker, PhD; Leah Roberts, BSc; Scott A. Beatson, PhD; Anton Y. Peleg, MBBS, PhD; Tiffany Harris-Brown, RN, MPH; David L. Paterson, MBBS, PhD; for the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)

JAMA. 2018;320(10):984-994

"Among patients with E coli or K pneumoniae bloodstream infection and ceftriaxone resistance, definitive treatment with piperacillin-tazobactam compared with meropenem did not result in a noninferior 30-day mortality. ."

JAMA | Original Investigation

Effect of Algorithm-Based Therapy vs Usual Care on Clinical Success and Serious Adverse Events in Patients with Staphylococcal Bacteremia

A Randomized Clinical Trial

Thomas L. Holland, MD; Issam Raad, MD; Helen W. Boucher, MD; Deverick J. Anderson, MD; Sara E. Cosgrove, MD, MS; P. Suzanne Aycock, MSN; John W. Baddley, MD, MSPH; Anne-Marie Chaftari, MD; Shein-Chung Chow, PhD; Vivian H. Chu, MD; Manuela Carugati, MD; Paul Cook, MD; G. Ralph Corey, MD; Anna Lisa Crowley, MD; Jennifer Daly, MD; Jiezhun Gu, PhD; Ray Hachem, MD; James Horton, MD; Timothy C. Jenkins, MD; Donald Levine, MD; Jose M. Miro, MD, PhD; Juan M. Pericas, MD, PhD; Paul Riska, MD; Zachary Rubin, MD; Mark E. Rupp, MD; John Schrank Jr, MD; Matthew Sims, MD, PhD; Dannah Wray, MD; Marcus Zervos, MD; Vance G. Fowler Jr, MD, MHS; for the Staphylococcal Bacteremia Investigators

JAMA. 2018;320(12):1249-1258.

Compared to standard therapy, algorithm therapy had:

-Noninferior efficacy

-Similar safety

-Significantly less antibiotics in short-course eligible pts

Proposal Subject	Clinical Requests	Registrational Trials	Strategy Trials 2018
Duration of IV antibiotics	5	0	2
Combination antibiotic therapy	3	0	2
Treatment of MDR Pathogens	3	0	1
Route of Administration	2	0	1

Differences in Registrational & Strategy Trials

	Registrational	Strategy
Purpose	Make new antibiotics available	Identify best treatment
Audience	FDA, EMA	Scientific Community
Study Design	Gram-positive: ABSSSI Gram-negative: cUTI	Answer clinical question
Consequences of failure	Compound scrapped +/- Company closes	Publish in lower impact journal
Cost	$$$$	$
Complexity	++++	+

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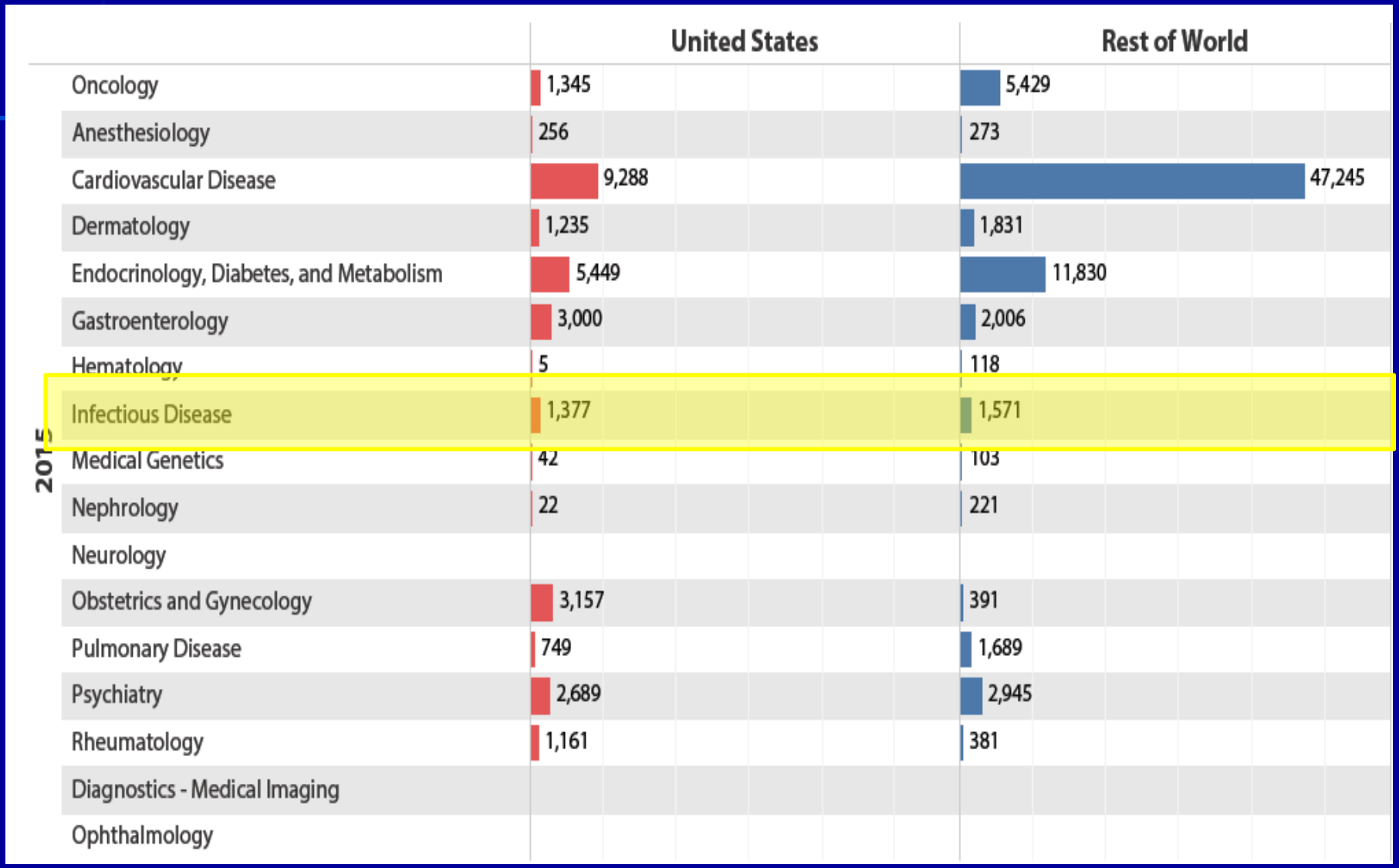
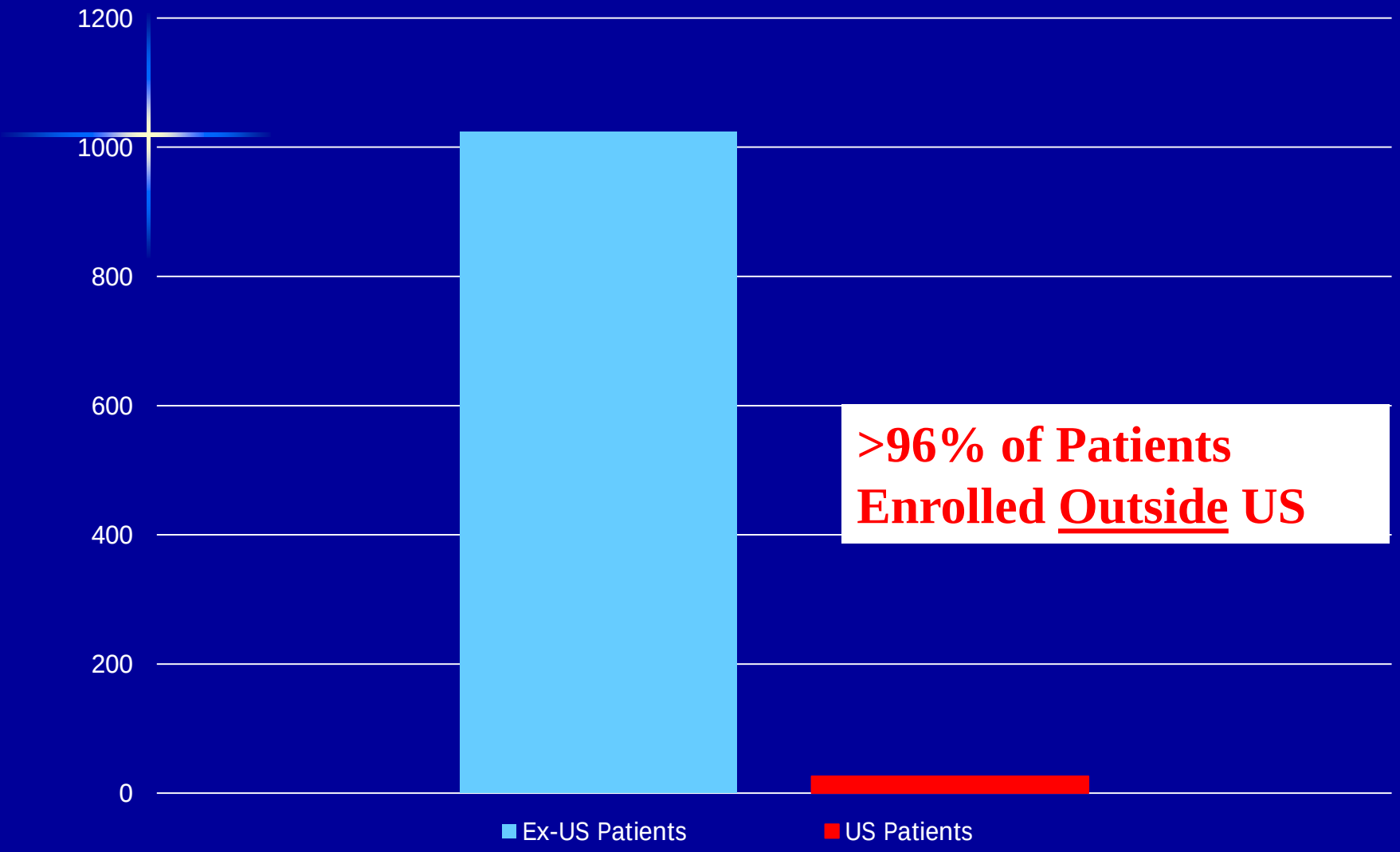
1. Most Patients in Clinical Trials are US



Global Participation in Clinical Trials Report 2015-16; July 2017. FDA Document

2. US Site Performance in ID Trials is Variable

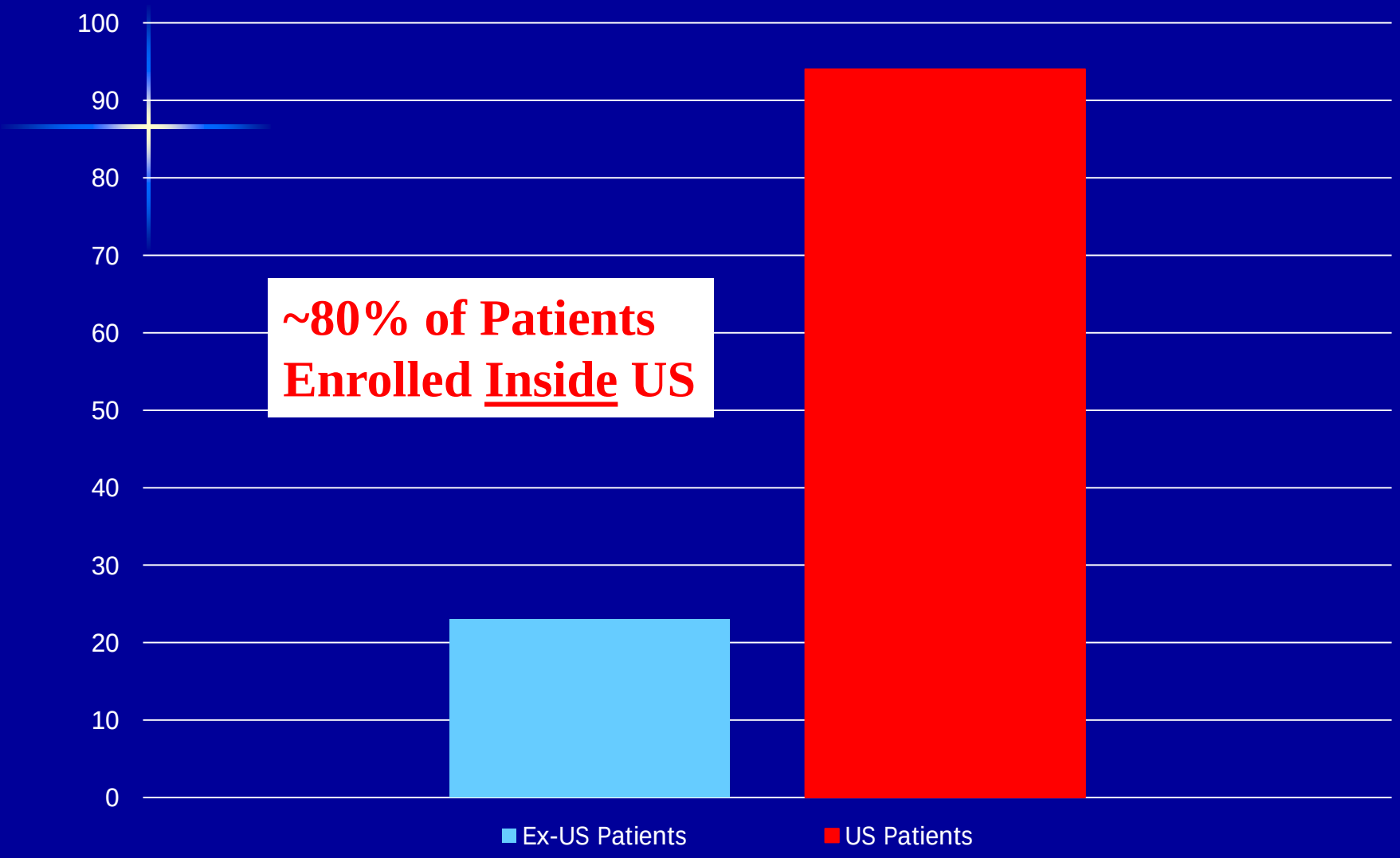
cUTI



>1000 Patients enrolled into 2 Phase 3 Identical Design cUTI Trials

2. US Site Performance in ID Trials is Variable

Adjunct Therapy for *S. aureus* Bacteremia



> 100 Patients in Phase 2 Exebacase *S. aureus* bacteremia

Fowler ECCMID 2019

What Makes a Study Enrollable in US?

	Success	Fail
Patients are there	ABSSSI	MDR-Resistant Pathogens (except ESBL, MRSA)
Integrate with clinical practice	Single-dose adjuncts	cUTI
PI "owns" disease	HABP/VABP	cUTI
Pathogens are there	ESBL, MRSA	Other MDR Pathogens
Patient comorbidity reasonable		VRE

Other Obstacles to US Site Based Research in Antibacterials

Insufficient trial volume to maintain site infrastructure

Site work academically undervalued

Bureaucracy

Partial Solution: Clinical Networks

- **Observational**

  Describe disease

- **Registrational**

  New drugs

- **Strategy**

  Best management

CLINICAL TRIALS TRANSFORMATION INITIATIVE

ARLG
Antibacterial Resistance Leadership Group

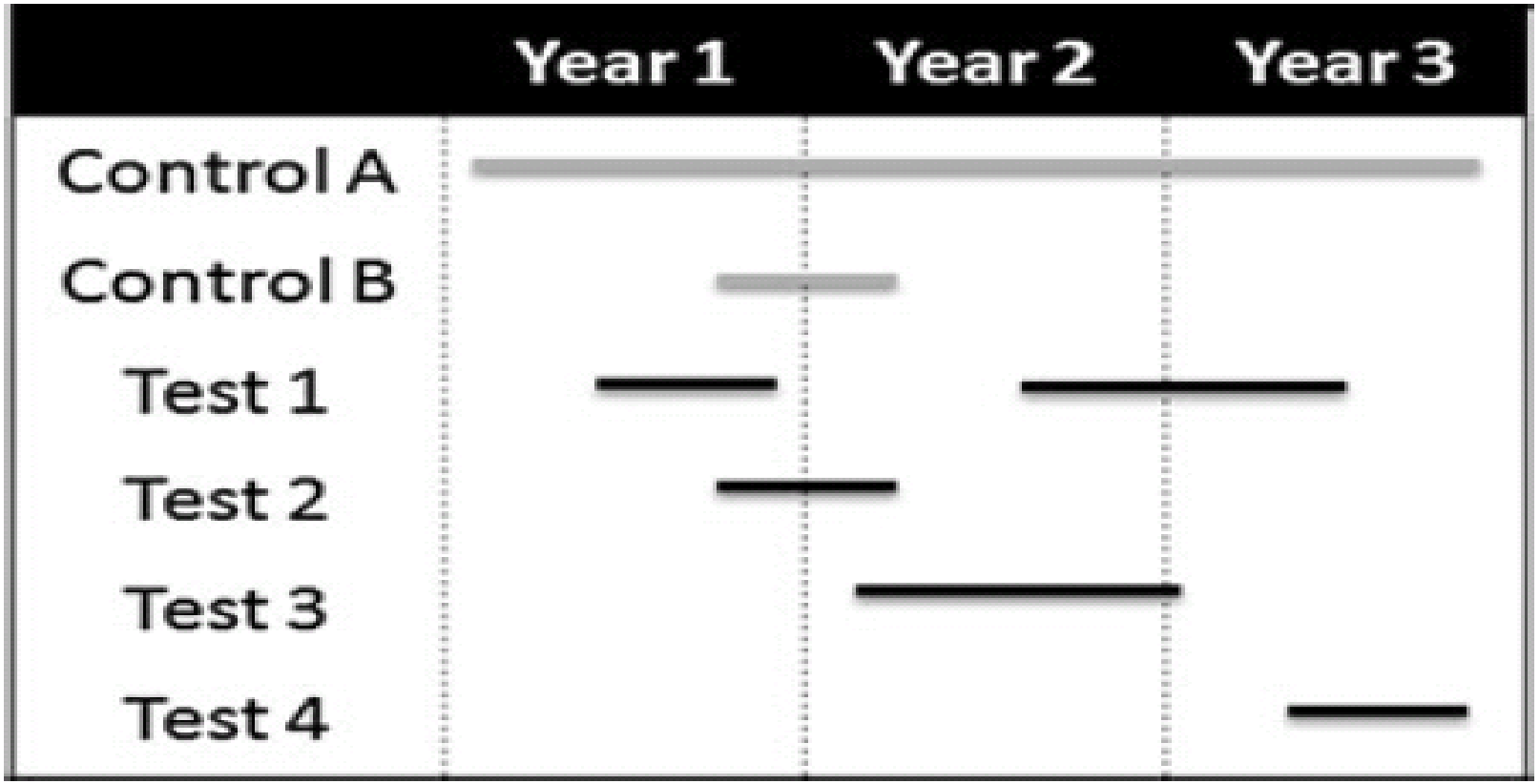
Registrational Trials Networks

Clinical Infectious Diseases

SUPPLEMENT ARTICLE

Efficient Delivery of Investigational Antibacterial Agents via Sustainable Clinical Trial Networks

Anthony McDonnell,[1] John H. Rex,[2,3] Herman Goossens,[4] Marc Bonten,[5] Vance G. Fowler Jr,[6] and Aaron Dane[7]

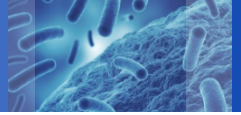


Registrational Site Networks

Pro	Con
Right Sites for Right Trials	Critical Mass of Registrational Trials
Maintain Trial Infrastructure	Sponsors May Not Use It

Strategy Trials Network

ARLG
Antibacterial Resistance Leadership Group



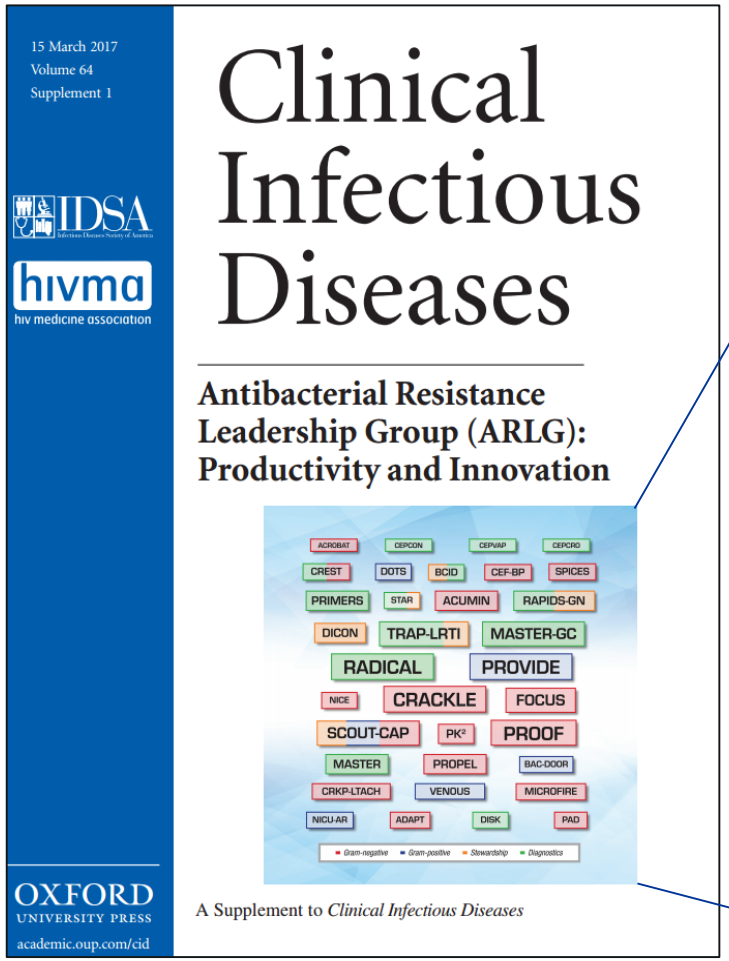
Antibacterial Resistance Leadership Group

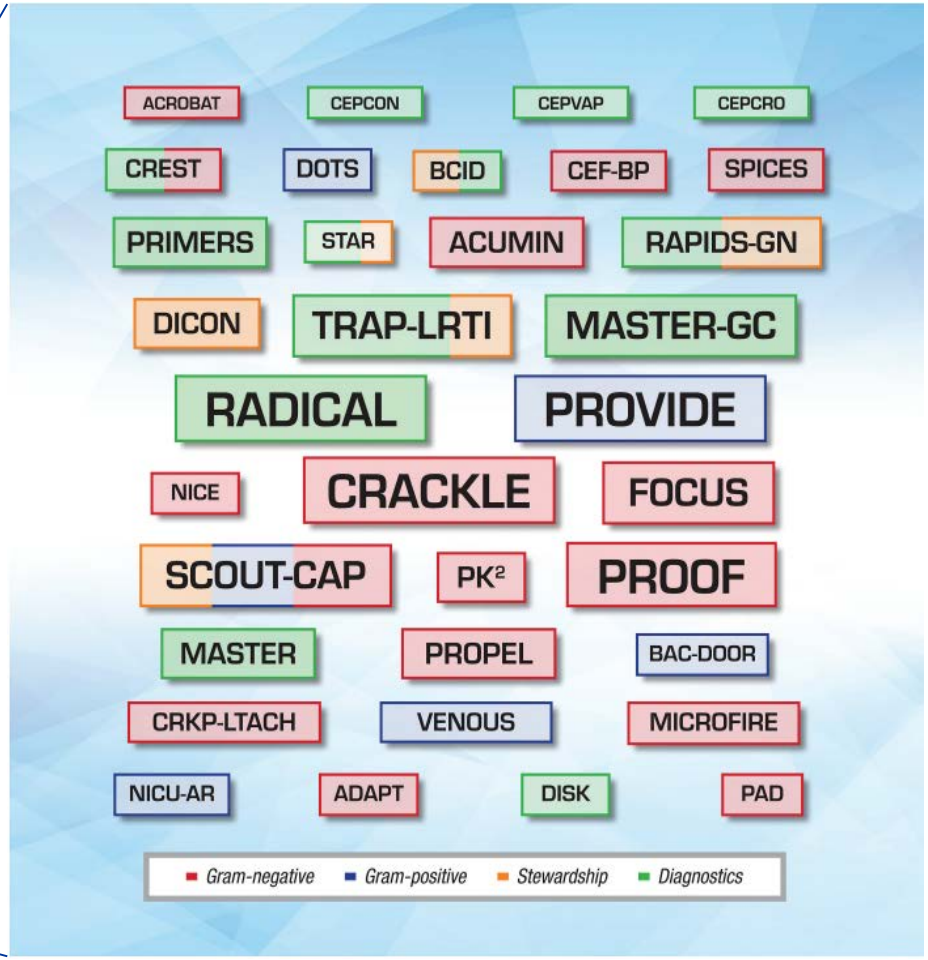
- **Purpose:** *To design, implement, and manage clinical research to change clinical practice and reduce the impact of antibacterial resistance*

- **Period 1:** *May 2014-Dec 2019* *>$60 million*
- **Period 2:** *Dec, 2019- Dec 2026* *$110 million*

- **Unique scientific and operational assets:**
  - Leadership and Operations Center (DCRI)
  - Statistics and Data Management Center (George Washington)
  - Laboratory Center (Mayo Clinic)
  - 50 national thought leaders on specialized committees

- **3 Emphasis Areas:** *Diagnostics; Clinical Trials; Relevant Science*





100+ proposals, 45+ studies, 100+ manuscripts, 130 sites/19 countries, 18,000+ subjects, 1400+ isolates shipped, 2 FDA approvals, 15+ therapeutic/60+ diagnostic companies, 36 mentees

Registrational vs. Strategy Networks

- Different functions
  - *Registrational: Make new treatments available*
  - *Strategy: Identify best treatments*
- Different audiences
  - *Registrational: FDA, EMA, etc.*
  - *Strategy: Scientific community*
- Different cost & complexity
- Similar Need for high quality US Sites

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Funding

FDA R18-FD005292

NIH R01-AI068804

NIH R01-HL119648

NIH U01-AI124319

NIH NO1-AI90023

NIH K24-AI093969

NIH UM1-AI1046811