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SUPPLEMENT ARTICLE

Transforming Concepts Into Clinical Trials and Creating a Multisite Network: The Leadership and Operations Center of the Antibacterial Resistance Leadership Group

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The Leadership and Operations Center (LOC) is responsible for facilitating, coordinating, and implementing the Antibacterial Resistance Leadership Group (ARLG) scientific agenda by engaging thought leaders; soliciting research proposals; and developing the processes, tools, and infrastructure required to operationalize studies and create and sustain the ARLG network. These efforts are ongoing as new projects are developed and the network expands and grows to address the ever-changing priorities in antibacterial resistance. This article describes the innovations, accomplishments, and opportunities of the LOC since the inception of the ARLG in 2013.

Keywords. antibacterial resistance; clinical trial network; infectious disease; mentoring.

The mission of the Antibacterial Resistance Leadership Group (ARLG) is to prioritize, design, and execute clinical research that will reduce the public health threat of antibacterial resistance. The Leadership and Operations Center (LOC) is responsible for facilitating, coordinating, and implementing the ARLG scientific agenda [1] by engaging thought leaders; soliciting research proposals; and developing the processes, tools, and infrastructure required to operationalize studies and create and sustain the ARLG network. The scientific agenda of the ARLG was developed by >50 key leaders in the field who constitute its committee membership. These experts have outlined the areas of greatest unmet need, established a scientific agenda, and formulated and evaluated potential clinical studies to address those needs. This internal expertise is supplemented by soliciting ideas from academia, government, and industry via a proposal portal on the ARLG website (http://arlg.org/how-to-apply).

The LOC is physically located within the Duke Clinical Research Institute (DCRI) in Durham, North Carolina. From this position, the LOC's coordination of ARLG committees, creation and implementation of the proposal portal, and handling of the corresponding application and review system allows for rapid decision making and implementation of proposed studies (Figure 1) [2, 3]. The review process for proprietary proposals is further expedited by the creation of a master Confidentiality and Disclosure Agreement (CDA) system covering committee members for discussion of all proposals. To date, >130 CDAs have been executed to enable ARLG discussions, >70 study proposals have been received and reviewed, and >30 proposals have been approved and implemented as ARLG studies.

CREATING AND MAINTAINING AN ARLG SITE NETWORK

An essential component for any study is identifying clinical sites with the appropriate patient population and resources to complete enrollment on time and within budget. This is particularly important in clinical trials targeting antibacterial resistance, where the utility of an individual site can be influenced by geographic variation in the prevalence of drug-resistant bacteria, national reimbursement trends that discourage the acknowledgement of specific types of nosocomial infections (eg, ventilator-associated bacterial pneumonia) [4], and local expertise that is often syndrome-specific. Accordingly, one of the first priorities of the LOC upon start-up was to create and develop a robust network of clinical sites. The ARLG site network was developed initially from the >37 000 sites that previously participated in DCRI studies, through the National Institute of Allergy and Infectious Diseases Vaccine and Treatment Evaluation Unit infrastructure, through site lists donated by industry partners from clinical trials, and through identification of new sites via the study feasibility process.

[a]Members of the ARLG Leadership and Operations Center are listed in the Appendix.

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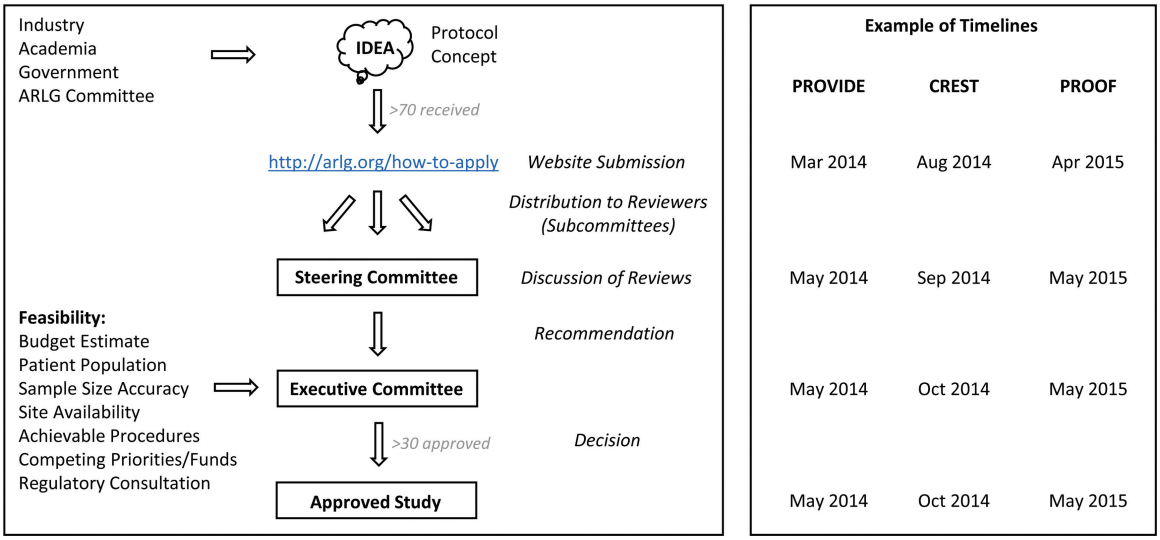

Figure 1. Antibacterial Resistance Leadership Group (ARLG) protocol concept receipt, review, and approval. Example timelines are shown for PROVIDE (Prospective Validation of the Vancomycin Exposure Profile Associated With Optimal Outcomes Among Patients With MRSA Bloodstream Infections) [2], CREST (Carbapenem-Resistant Enterobacteriaceae in Solid Organ Transplant Patients), and PROOF (Pharmacokinetics, Pharmacodynamics and Safety/ Tolerability of Two Dosing Regimens of Oral Fosfomycin Tromethamine in Healthy Adult Participants) [3]. PROVIDE and PROOF concepts were generated by ARLG committees and submitted directly to the ARLG Steering Committee in response to a call for proposals. CREST was submitted via the ARLG website by the CREST investigators.

More than 300 detailed site questionnaires have been received by the ARLG thus far, including estimated numbers of cases of key infections and details of typical standards of care, and the site network continues to grow and expand as new sites are identified and approached. The work required to create and maintain a large clinical trial network (Table 1) [5] and to operationalize ARLG studies (Figure 2) [2, 3] is extensive: >100 DCRI staff have played a role in building the ARLG network and operationalizing ARLG studies to date.

Efficient coordination of such a large network has been facilitated by a number of innovations. First, a database was created to allow querying of feasibility data for each specific ARLG study as it arises. Next, operational innovations such as the DCRI Rapid Start Network (RSN) provide significant time savings. For RSN sites, an initial master agreement outlining general terms is executed far in advance of a specific project need. A study-specific addendum is then added for each study with the individual protocol and study budget included. On average, this reduces site agreement negotiation by 2 months. To date, the DCRI has put in place >140 National Institutes of Health (NIH) grant–specific master RSN agreements.

Table 1. Components Required to Support the Antibacterial Resistance Leadership Group Network

Department and Component	Purpose	No. to Date
DCRI Contracts Department		
Subawards/agreements	Contract with committee chairs, center directors, vendors, sites	>160
Confidentiality and disclosure agreements	Receive investigational product data from companies and share with committee members for assessment of study proposal priority and viability	>130
Data use agreements	Enable data mining and modeling	8
Material transfer agreements	Facilitate disbursement of bacterial strains from the ARLG Virtual Biorepository [4]	10
DCRI Business Development and Duke Office of Research Administration		
Subpacket collection	Preparation for subawards	>100
Ballpark budgets	Pricing estimates to assess feasibility of proposed studies	>26
Full study budgets	Detailed budgets allow correct allocation and efficient use and tracking of funds	>28
Progress reports and noncompeting renewals	Annual compliance with NIH grants policy	4 y × ~200 pages
DCRI Sponsored Projects Administration and Duke Office of Sponsored Programs		
Project-specific and overall grant financial reports	Monitor grant expenditures and compliance	>$35M total funds managed
Invoice processing	Facilitate payment of chairs, directors, vendors, sites	>600

Abbreviations: DCRI, Duke Clinical Research Institute; NIH, National Institutes of Health.

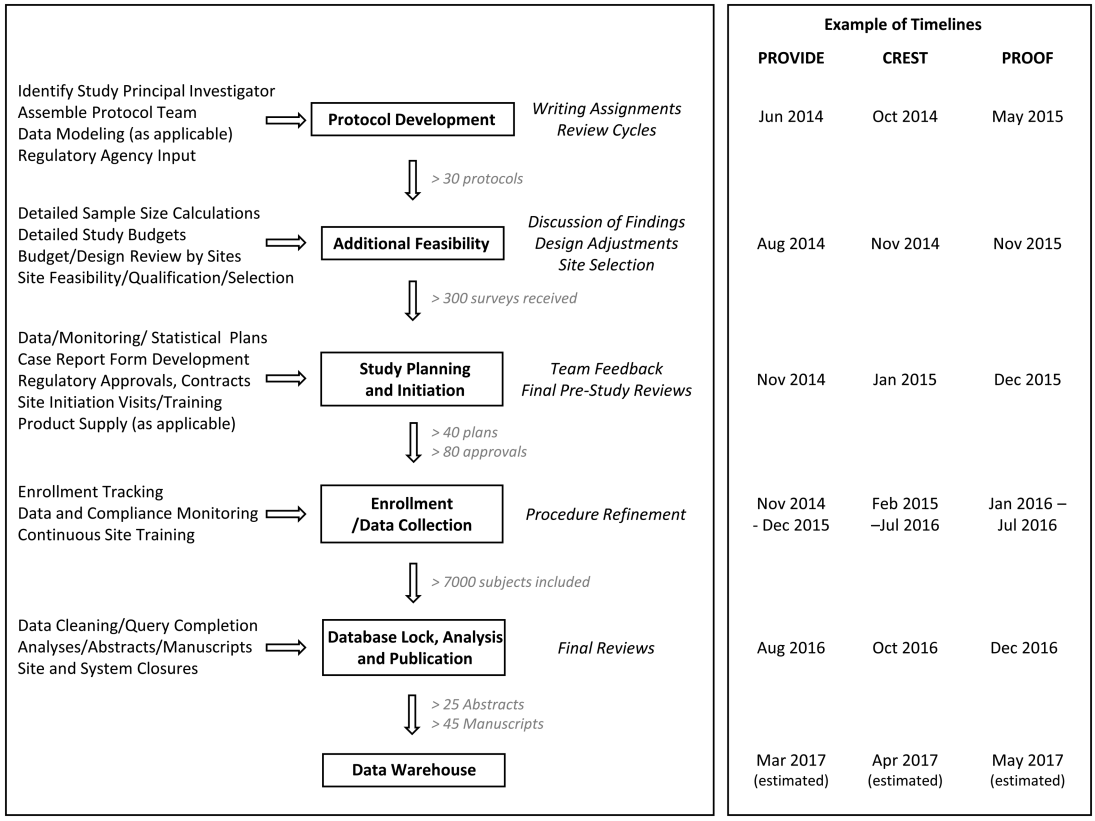

Figure 2. Antibacterial Resistance Leadership Group (ARLG) protocol development and study execution. Example timelines are shown for PROVIDE [2], CREST [3], and PROOF [2]. PROVIDE (n = 305) and CREST (n = 170) are noninterventional studies. PROOF is an interventional phase 1 study (n = 19). See Figure 1 legend for study descriptions.

CREATING AND CONNECTING INFECTIOUS DISEASE CLINICAL TRIAL NETWORKS

Clinical trials in antibacterial resistance, or for new antibiotics, have failed to keep pace with need [6]. This, coupled with rapid emergence of resistant pathogens in a wide variety of disease states with often low prevalence [7], is a significant challenge for operationalizing infectious disease clinical trials. A large network of highly experienced clinical trial sites with sufficient patient populations to address all resistance pathogens in all disease states in both inpatient and outpatient settings did not exist when the ARLG was formed. As such, the ARLG has sought to cultivate networks that can be harnessed for antibacterial research.

For example, CRACKLE (Consortium on Resistance Against Carbapenems in *Klebsiella pneumoniae* and Other Enterobacteriaceae) is an ARLG network developed by van Duin et al [8], which now includes 17 states across the United States as well as sites in Colombia. In addition to findings regarding the epidemiology, outcomes, and impact of carbapenem-resistant Enterobacteriaceae (CRE) molecular characteristics in CRE-infected patients, as summarized by Doi et al [3], CRACKLE and CRACKLE II have enabled assessment of risk factors, frequency, geographic location, and clinical characteristics of CRE-infected patients. These data are being utilized to inform realistic inclusion/exclusion criteria, assist in early consenting procedures, and identify appropriate clinical sites for the ARLG's planned interventional CRE studies. Additional plans are underway to include data from patients infected with *Pseudomonas aeruginosa* and *Acinetobacter baumannii* to inform design of interventional clinical trials addressing these key pathogens.

In addition to creating new networks, the ARLG has leveraged existing networks like the Duke Infection Control Outreach Network (DICON) and Duke Antibiotic Stewardship Outreach Network (DASON) to conduct a first-in-kind study, DICON I [9], of antimicrobial stewardship in a community hospital setting. DICON I is now being expanded to DICON II [9] to introduce research capabilities to additional community hospitals, in which the majority of US patients receive their care but where few research studies are conducted [10].

The ARLG is also closely affiliated with the hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) risk factor and pilot studies from Duke's Clinical Trials Transformation Initiative [11]. These projects—collaborations between academia, the US Food and Drug Administration, and industry—aim to develop and utilize novel techniques, such as consenting

Table 2. Antibacterial Resistance Leadership Group Early-Stage Investigator Seed Grants

Study Name	Description	Status
BCID	Assessment of clinical and economic outcomes of the rapid FilmArray blood culture identification panel test for gram-positive bloodstream infections	Complete [15]
CEF-BP	Ceftriaxone breakpoints—a gram-negative database to establish clinically relevant antibiotic breakpoint interpretive criteria for ceftriaxone	Complete [16]
CRKP-LTACH	Study of carbapenem-resistant *Klebsiella pneumoniae* in long-term acute care hospitals	Analysis phase
VENOUS	Cancer patients with vancomycin-resistant *Enterococcus faecium* bacteremia—prospective evaluation of clinical outcomes	Protocol development
MICROFIRE	Study of microbiota colonization in the presence of intestinal fluoroquinolone-resistant *Escherichia coli*	Protocol development

at-risk patients at the time of intensive care unit admission for enrollment into a trial should HABP or VABP develop, to increase the feasibility of these extremely challenging trials. The risk factor study, which has already enrolled >3000 subjects, also provides data that can inform realistic inclusion/exclusion criteria and identify appropriate clinical sites for the types of interventional pneumonia trials that the ARLG is planning.

The ARLG is also collaborating with Duke's Pediatric Trials Network (PTN) to assess the pharmacokinetics of a novel aminoglycoside in the pediatric population [3]. The PTN was created in response to the Best Pharmaceuticals for Children Act to provide pediatric clinical trial data on products commonly used in the pediatric population yet not approved specifically for such use [12]. To date, the PTN has completed 11 clinical trials in >4000 patients, including trials of several antibiotics. As such, the network serves as a valuable source of experienced clinical trial sites for ARLG pediatric infectious disease studies.

In addition, the ARLG is in discussions with the Innovative Medicines Initiative–funded Combatting Bacterial Resistance in Europe (COMBACTE) project to collaborate with its pan-European clinical trial network (CLIN-Net) and has actively initiated collaborations with networks in Colombia [13], Chile, Argentina, Brazil, Mexico, Asia, Australia, and New Zealand [14]. Future collaborations with the International Collaboration on Endocarditis and the critical care clinical trial networks in Canada and Australia/New Zealand are also envisioned. Laboratory-based collaborations with China and India are also in discussion, which may also ultimately lead to ARLG clinical trials in those regions.

FOSTERING THE NEXT GENERATION OF INFECTIOUS DISEASE CLINICAL INVESTIGATORS

Another key focus of the ARLG is mentoring. Providing infectious disease fellows and junior faculty with research opportunities and mentoring in clinical trials is crucial to the future of antibacterial resistance research. The ARLG LOC has a Mentoring Committee dedicated to supporting and nurturing new investigators through 3 types of training opportunities: early-stage investigator (ESI) seed grants, the ARLG fellowship, and mentee involvement in ARLG projects.

To date, 5 ESI seed grants have been awarded (Table 2) and there are currently 26 mentees participating in 16 ARLG studies. The ESI seed grants in particular are designed to allow researchers to generate preliminary data leading to additional external funding. Recipients of the 3 initial seed grants have received subsequent grants outside of the ARLG and their ARLG-funded work has been published in high-profile journals [15, 16]. Altogether, 13 ARLG abstracts and 12 ARLG manuscripts have included mentee authors.

COMMUNICATING ARLG OPPORTUNITIES AND PROGRESS

Communication of the ARLG scientific agenda, opportunities, progress, and study findings has been accomplished via a website (http://arlg.org/), at meetings, and in presentations and publications. Formation of the ARLG publication committee and its corresponding process has facilitated publication approval, tracking, and compliance with the NIH Public Access Policy. To date, >45 manuscripts have been published and 25 abstracts have been presented from ARLG work.

CHALLENGES AND FUTURE DIRECTIONS

The ARLG LOC has successfully developed new innovative processes, collaborations, and mentorships to create and sustain a research network and its associated clinical trials. The LOC will continue to innovate in order to address the challenge of operationalizing the more complex multinational studies that are currently being developed. With the inevitable emergence and spread of new resistant pathogens, the LOC will facilitate the ARLG scientific agenda to ensure that the most critical priorities in antibacterial resistance are being addressed.

Notes

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APPENDIX

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