

Late-breaking update (May 2016):

Since the workshop in January, key achievements include:

- Continuous exchange between existing US and EU networks for the conduct of clinical trials related to antimicrobial resistance has taken place, resulting in alignment between US and EU capabilities and an increase in sharing of experiences in conducting multidrug resistance trials. Specifically, a test case is ongoing on how alignment of US and EU clinical trial structures could help meet patient enrolment goals. Through IMI's networks CLIN-NET and LAB-NET, established by the COMBACTE project under the ND4BB programme, suitable clinical sites are being identified to participate in one of the ongoing NIH/NIAID targeted clinical trials on multidrug resistance.
- The discussions at the workshop have helped to better understand the capabilities of the existing networks to answer key questions and conduct different types of clinical trials with antibiotics, i.e. trials directed at MDR pathogens vs more standard registrational trials for new antibacterial drugs. This has catalysed further dialogue among the various stakeholders both in the US and in Europe on the need for facilitating the latter. Also, this workshop was instrumental in helping the participants to understand that there are multiple models for infrastructures to conduct clinical trials, both existing, and contemplated, and it is important to differentiate and distinguish which model one has in mind.

Report of the Workshop on Transatlantic collaboration on clinical trials related to antimicrobial resistance

21–22 January 2016, Sheraton Stockholm Hotel, Stockholm, Sweden

About this report

A workshop "Transatlantic collaboration on clinical trials related to antimicrobial resistance" was held in Stockholm on 21-22 January 2016. This report summarises the discussion at the workshop and presents the key conclusions and recommendations that were made to overcome the identified barriers for the efficient conduct of high-quality global antibacterial clinical trials. Input from different stakeholders from the US, Canada and Europe was received, e.g. academic clinical investigators, large pharma, small- and medium-sized companies, and relevant funding organisations. The workshop was an important first step towards actions that could be taken collectively and individually to overcome the barriers identified. Important opportunities to ensure a better alignment of existing networks and resources were identified. Follow-up on these opportunities will now be required in order to take key concepts discussed and suggestions made to a next level.

Introduction

The workshop, organised by the Innovative Medicines Initiative (IMI) in collaboration with the National Institutes of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAID), the European Commission (EC), the Joint Programming Initiative Antimicrobial Resistance (JPIAMR) and the IMI project

COMBACTE was attended by over 60 invited participants representing various funding organisations/initiatives, large and small companies, academic researchers, regulators, and clinicians from EU, US and Canada involved in clinical trials against antimicrobial resistance ([Appendix 1 participants list](#)).

The workshop objectives were:

- to share information on current existing initiatives for clinical trial networks for antimicrobial resistance, in order to learn from each other and avoid duplication of efforts;
- to discuss challenges and opportunities to overcome barriers for the efficient conduct of high-quality global clinical trials;
- to foster opportunities for collaboration between the different networks and initiatives in the EU, US, and CA to facilitate clinical research in our fight against AMR;
- to produce concrete deliverables and action points towards solutions and recommendations to overcome the barriers identified through better alignment of existing networks and resources.

To reach these objectives, the workshop was divided into different sessions leaving plenty of opportunity for plenary discussion ([Appendix 2 Agenda](#)).

Several key organisations are supporting research in the fight against antimicrobial resistance; however the funding opportunities and the research goals vary depending on organisation's mission and structure. The key funding organisations present at the workshop were therefore briefly presented during the working dinner on 21 January to ensure that all participants had a good understanding of their remit when moving into the discussions (Annex).

Opening session

The meeting was opened by words of welcome by Pierre Meulien, IMI, and Mats Ulfendahl, JPIAMR. Dennis Dixon, NIH, presented the objectives of the meeting stressing the theme 'What can we do better together that we are struggling to do alone?' ([Appendix 3](#)). John Rex, in his keynote lecture, set the scene speaking about clinical research on AMR highlighting the current pipeline, development issues, and ideas for ways forward ([Appendix 4](#)). The pipeline is precarious with not only a limited number of agents under development but more important, only a very limited diversity in the mechanisms of action. Currently there is a focus on providing clinical data on agents to treat infections that are multidrug resistant (MDR) to other existing antibiotics. However these studies are very difficult to conduct. Relevant clinical and safety data can also be generated from quality registrational trials conducted in patients with recognised infections due to bacteria that are susceptible to the new agent but are of a more prevalent usual drug resistance (UDR) rather than the rarer MDR/XDR. A concept of a dedicated clinical trial platform supporting indication-specific trials to gather quality registrational data on new agents on a rolling basis was proposed.

Session 1: EU and US clinical trial networks for the development of treatments against antimicrobial resistant infections

Session 1 focused on the status and ongoing activities of existing EU and US clinical trial networks. Marc Bonten presented the different networks of the COMBACTE projects under the IMI New Drugs for Bad Bugs (ND4BB) programme, i.e CLIN-NET (clinical networks and sites), LAB-NET (laboratories), STAT-NET (methodological) and EPI-NET (epidemiological). Considering the nature of the compounds being tested in clinical trials in the programme, the activities of the networks focus so far on MDR ([Appendix 5](#)). Chip Chambers presented the Antibacterial Resistance Leadership Group (ARLG) whose efforts focus on several areas of drug resistance, including Gram-negative resistance, Gram-positive resistance, diagnostics and antimicrobial stewardship ([Appendix 6](#)).

Session 2: Lessons learned and opportunities for optimising the conduct of global clinical trials to address antimicrobial resistance

The focus of session 2 was on lessons learned and opportunities for optimising the conduct of global clinical trials to address antimicrobial resistance. The session started with three presentations. Dennis Dixon presented ongoing and completed NIAID trials on antibacterial resistance highlighting the issues faced with real world trials, the solutions adopted, and the lessons learned ([Appendix 7](#)). Hasan Jafri shared experiences from conducting interventional trials in the IMI COMBACTE projects highlighting how the collaborative public-private model is well suited for R&D in novel, difficult to study populations with limited or no regulatory precedent ([Appendix 8](#)). Herman Goossens focused on the specific challenges of clinical sites selection (e.g. obtaining accurate data on resistance rates) and patient enrolment drawing from the experience of COMBACTE ([Appendix 9](#)).

Points made during the panel discussion:

- The speakers and many participants recognised the need for high quality high expertise (GCP-trained) networks and harmonised procedures for conducting clinical trials with new and existing antibiotics and other agents addressing bacterial infections.
- It was appreciated that these could include both a focus on trials to treat MDR/XDR pathogens (as the current COMBACTE networks do) as well as on standard trials for key indications (independent of pathogen).
- Although there is a clear public health unmet need, studies in MDR/XDR are difficult and risky. Challenges include among others the sporadic and episodic nature of many of the relevant infections, the need for robust epidemiology data, the issue of identifying the organism early enough for enrolment in a trial, obtaining informed consent, and lack of appropriate expertise including academic research organisations/contract research organisations (AROs/CROs). Although recognising the challenges, conducting such studies in MDR/XDR remains an option according to Marco Cavaleri, EMA. For antibacterial agents not yet licensed, Ed Cox, FDA, stressed the importance to balance the need to conduct studies in MDR/XDR with the risk of failing a promising compound because of the pathway selected being too difficult. Dialogue with the regulators is therefore important to ensure that the best strategy is adopted for developing a novel antibacterial agent.
- Performance management, especially in the context of site evaluation and patient outcomes, would be important to conduct, and lessons learned during the process of site selection and patient enrolment should be shared in a transparent way.
- Ideas around common protocols (or a master protocol), increased collaboration, common standards, improved standards, common comparator and shared control groups were welcomed by many workshop participants. This would clearly optimise the efficiency in clinical trials. In this regard, it was suggested that a lot could be learned from the oncology field. Still others pointed out the differences between oncology and infectious diseases in the key areas of challenge.
- In discussing the possibility of a single standard Phase 3 protocol to support multiple drugs, concerns were raised regarding the ability to standardize inclusion and exclusion criteria. It was noted that standardisation was more challenging for Phase 3 trials than for Phase 1 and 2 trials, especially in the context of exclusion criteria, and that 'harmonisation' might be more realistic terminology. However, it was also noted that a 'harmonization' approach may defeat some benefits that would be obtained with a single, standard protocol.
- Networks in general have a role to play in creating collective intelligence to learn from individual failure, to avoid replication and to propose innovative approaches for clinical development. Alignment of current networks was considered important in view of a global network. Networks have a role to play both for the conduct of trials designed for registration of new products and for optimizing treatment of individual patients with existing products.

- There is a need for better epidemiology/clinical epidemiology at global level. Issues related to competing trials, and competing enrolment should be taken into consideration as well as the use of rapid test diagnostic for enrichment strategies.
- A network for the testing of rapid diagnostic tests should also be considered.
- MDR is also common in neonates and other specific patient groups that present specific challenges that should also be addressed.

Session 3: Way forward

The objective of Session 3 was to work out concrete action points towards solutions and recommendations to overcome the barriers identified and facilitate collaboration for the conduct of global clinical trials on AMR.

Practical examples of planning a global clinical collaborative study were presented: the first example related to a collaboration between the Clinical Trials Transformation Initiative (CTTI) and COMBACTE CLIN-NET on a pilot study that will lead to improved HAP/VABP clinical trial feasibility ([Appendix 10](#)). The concept of up-front work with consent and pre-enrolment to optimise the study is being tested, and CTTI is collaborating with CLIN-NET to identify clinical sites in EU. The second example related to the clinical development of Aztreonam-avibactam, that is supported by both IMI in the context of the project COMBACTE-CARE and BARDA ([Appendix 11](#)). A panel discussion followed during which the points below were made.

Points made during the panel discussion:

Networks

- Different types of networks exist, and others are needed. One size does not fit all. Yet, wherever possible, alignment of existing networks to reach overlapping goals is worth exploring.
- One example of alignment was introduced in Session 2 where alignment of US and EU network structure could help reach enrolment goals in one key study on MDR Gram negative bacteria underway. Efforts at the meeting have led to a test case for this possibility with the trial discussed.
- An opportunity exists to utilize existing clinical trials infrastructure to answer key questions and test products to address AR. Consideration should be given to how increase communication and collaboration between networks to better align work on both sides of the Atlantic. This includes sharing lessons learned, teaming as appropriate, and harmonizing where possible.
- Clinical trial networks and infrastructure should be strengthened but should not replicate the CRO model. In other words, there needs to be a central point of scientific direction to guide the implementation of the studies. Consideration should be given to agree on a common network definition.
- The ARO/ CROs capabilities should be developed with the right competencies for AMR trial design, which needs to be flexible and innovative.
- As a first step, existing capabilities for the conduct of clinical trials with the current network structures should be assessed. Only if gaps are identified, new networks may need to be developed. Performance indicators would be useful to assess the added value of networks.
- Ideally, networks should benefit the whole community, including large and small companies and should include scope for diagnostic tools. In particular, the role of small and medium-sized enterprises and opportunities for engagement for them, e.g. in the COMBACTE networks, should be further clarified.
- Networks should be representative of the populations physicians treat including for example paediatric patients, the elderly, or critically ill patients. There is a need for the networks to generate data in these patient populations to support evidence based treatment decisions. Not only this presents further challenges to be considered but there also may be a need for specific expertise to support the enrolment of such populations in trials e.g. psychologists.
- There should be greater engagement from the clinical research community and healthcare providers.

- The diagnostics industry should be more integrated into the current discussion on networks for AMR as there seems to be consensus that there is a place for rapid diagnostic tests in the intervention strategies discussed. There is a need for further considerations on how best to achieve this.

Sustainability

- There is a need to address the maintenance and sustainability of networks post initial funding. In that context, the point was made that IMI is successful as a catalyser, but there is an expectation that funded activities should develop sustainability plans and become independent of IMI funding. National governments would have a role to play. The need for a working group to strategise about this should be further discussed.

Patient engagement

- Patients should be involved in the network as well as in the discussions at a more strategic level.

Cooperation on sharing/learning.

- Considerations should be given to enhancing the 'learning' aspects of current and future networks so that knowledge gained in one network, such as negative results or proven 'best practices' are shared proactively with the broader research community.
- There was agreement that sharing SOPs, process and operational aspects of trial implementation could be helpful to move the field forward. In addition, there may be value in soliciting qualitative research on recent and ongoing trials in this area to better define and disseminate what works well and what does not.
- Need for further discussion about contracts with trial sites. Possibility of having a working group set up to see if contracts could be harmonised to be explored.

Joining the funding forces

- A suggestion for a Funders Forum to look at an overall strategy to support trials and potential collaborations, including funding approaches (along the line of the experience with influenza) was made. Support from national governments should be sought.

Towards a virtual global network

- Opportunities should be explored for expanding more globally and including countries where the incidence of AMR may be far greater than in western hemisphere. For instance there are some networks in China, Vietnam with which it could be of value to partnering on scientific level.

Outputs of the workshop, recommendations & next steps

The workshop successfully brought together participants representing the various stakeholders committed to collaborating to overcome the barriers for conducting clinical trials related to antimicrobial resistance. In particular, the level of discussion and input not only from the speakers and panellists, but from the entire audience showed the engagement and commitment by all to progress to concrete actions.

This workshop was an important opportunity for recognising similar lessons learned and difficulties experienced by the various groups. It also set the grounds for ARLG and CLIN-NET/LAB-NET to exchange and align for an increased collaboration, as well as for further exploration of a joint clinical trial network.

This workshop was the first meeting of its kind, and the outcome of the meeting will now very much depend on follow-up to convert the recommendations made into concrete actions, for instance through working groups to address more specifically the key action points identified as well as follow-up meetings to review progress and plan ahead.

The discussions resulted in a number of concrete next steps that should be explored.

Short term actions:

1. Explore linkage and further collaboration between the existing networks in the EU, US, and Canada to help with the conduct of currently ongoing clinical trials.
2. Explore the value of working groups to progress specific recommendations, e.g. a working group on information and documentation sharing between existing networks, a working group looking at the design of a joint clinical trial network.

Medium and longer term actions:

1. Driven by a working group 'Information and documentation sharing': Identify and collect material to be shared between current networks, e.g. protocols, information about study sites. Explore options and identify the best place to store such material (the ND4BB Information Center would be one possible solution).
2. Driven by a working group 'Joint clinical trial network': In a first step, work out a clear understanding of the need of different stakeholders, including small- and medium-sized companies, large companies, clinical investigators, patients, regulators. Then, assess the currently existing infrastructure (e.g. the ND4BB networks in Europe, ARLG in the US, Canadian networks) to identify potential gaps and actions towards a joint network. Such a joint clinical trial network could serve both trials targeted for MDR/XDR pathogens (as the current COMBACTE networks do) as well as standard trials for key indications (independent of resistant pathogen).
3. A Funder's forum? Considerations should build on existing structures such as the Transatlantic Task Force on Antimicrobial Resistance (TATFAR).

Annex

European Commission has several mechanisms to support antimicrobial resistance research:

- Research and innovation projects; SME instrument
- Inducement prize for the better use of antibiotics prize awarded for developing a rapid test to identify, at the point of care, patients with upper respiratory tract infections that require antibiotics and those that can be treated safely without antibiotics
- European Investment Bank (EIB)/ European Commission (EC) – InnovFin – Infectious Disease Finance Facility (IDFF). Risk-sharing loan schemes offered to EU organizations developing vaccines, drugs, medical and diagnostic devices, and research infrastructures for combatting infectious diseases; Targets projects passed the pre-clinical stage and seeking clinical validation.
- The European & Developing Countries Clinical Trials Partnership (EDCTP) funds collaborative research that accelerates clinical development of new or improved treatments for key poverty-related infectious diseases; many studies focus on AMR;

<https://ec.europa.eu/programmes/horizon2020/h2020-sections>; <http://www.edctp.org/>

Joint Programming Initiative on antimicrobial resistance (JPIAMR) coordinates national funding from 22 countries (including Canada, Japan) and supports collaborative action to fill existing knowledge gaps in AMR; A Strategic Research Agenda (SRA), which outlines key [neglected] areas to tackle, guides JPIAMR and provides framework for future investment in research priorities. The SRA also serves as a guidance documents for nations to align their AMR research agenda. JPIAMR supports projects through annual calls for proposals. <http://www.jpiaamr.eu/>

Innovative Medicines Initiatives (IMI) is a public-private partnership between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA), with the objective to improve the drug development process and to accelerate the development of better, safer medicines for patients. IMI works by forging collaborative partnerships involving key stakeholders in medical research, including the pharmaceutical industry which provides contribution as in-kind and partners such as universities, small and medium-sized enterprises (SMEs), patient groups and regulatory agencies who can receive funding. New Drug for Bad Bugs (ND4BB) is an IMI programme that is addressing key challenges from early discovery to development of new medicines against AMR <http://www.imi.europa.eu/>
<http://www.imi.europa.eu/content/nd4bb>

COMBACTE (NET, MAGNET and CARE) are three public-private consortia within the IMI ND4BB programme addressing clinical development challenges for antibacterial agents to combat AMR. COMBACTE-NET is developing a European wide clinical (CLIN-NET) and aligned laboratory (LAB-NET) networks to build a sustainable capability to evaluate clinical interventions to address antibiotic resistance.
<http://www.combacte.com>

NIH/NIAD conducts and supports basic and applied research on many aspects of antimicrobial (drug) resistance, including basic research on how microbes develop resistance, new and faster diagnostics, and clinical trials designed to find new vaccines and treatments effective against drug-resistant microbes. The Division of Microbiology and Infectious Disease (DMID) is the division responsible for providing funding opportunities and resources for researchers that support basic research, preclinical development, and clinical evaluation of antibiotics. Specifically, DMID's standing clinical trials infrastructure includes the [Phase I Clinical Trial Units](#) for Therapeutics, the [Vaccine and Treatment Evaluation Units](#) and the Sexually Transmitted Infections Clinical Trials Groups.
<https://www.niaid.nih.gov/topics/antimicrobialresistance/Pages/default.aspx>.

Led by Duke University, the antibacterial Resistance Leadership Group (ARLG) develops, designs, implements, and manages a clinical research agenda to increase knowledge of antibacterial resistance.

In addition, DMID has a series of [Targeted Clinical Trials to Reduce the Risk of Antibacterial Resistance](#) underway and completed. These are related, but independent trials addressing optimisation of off-patent antibiotics in the hopes of reducing the risk of antibacterial resistance.

The Biomedical Advanced Research and Development Authority (BARDA), within the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services provides medical countermeasures that address the public health and medical consequences of chemical, biological, radiological, and nuclear (CBRN) accidents, incidents and attacks, pandemic influenza, and emerging infectious diseases. In this respect BARDA enters into public-private partnerships to support development of therapies against antimicrobial resistance.

<http://www.phe.gov/about/BARDA/Pages/default.aspx>

The Clinical Trials Transformation Initiative (CTTI), which was established by the US Food and Drug Administration and Duke University is a public-private partnership to identify and promote practices that will increase the quality and efficiency of clinical trials. CTTI has initiated the three projects and workstreams to address different aspects of the antibacterial drug development crisis.

<http://www.ctti-clinicaltrials.org/what-we-do/ctti-project-categories/ab-drug-development>

Canadian Institutes of Health Research (CIHR)/ Institute of Infection and Immunity (III) CIHR-III provides funding opportunities to supports research and helps to build capacity in the areas of infectious disease and the body's immune system; AMR is a primary strategic objective of the CIHR-III; including funding opportunities on novel approaches to antibiotic resistance .

<http://www.cihr-irsc.gc.ca/e/40485.html>