Enabling AMR-related Clinical Trials in India: Network Exploratory Workshop
Conference Hall, Second floor, ICMR Headquarters, New Delhi

On 25–26th November 2019, the Indian Council of Medical Research (ICMR) and the Global Antibiotic Research and Development Partnership (GARDP) organized a two-day workshop to map out the opportunities, challenges and practicalities of carrying out phase II/III/IV clinical trials of new antibiotics in India. Held at the ICMR headquarters in New Delhi, India, the workshop brought together stakeholders from the Indian research, clinical, biotech and regulatory communities, as well as representatives from regulatory bodies in the USA, Europe and Japan, to discuss the current state of global antibiotic development with emphasis on the potential for India to make a greater contribution to the global and local development by taking a greater role in the clinical evaluation of new treatments.

The specific objectives of the workshop were to:

- Understand the regulatory requirements and operational challenges of antibiotic clinical trials to evaluate antibiotics for patients with multi-drug resistant infections
- Identify the capacity development required to carry out pathogen-specific and regulatory standard clinical trials in India.
- Explore the potential for tertiary hospitals in the ICMR network to become the initial sites of a pilot AMR Clinical Trial Network, co-sponsored by GARDP to evaluate new treatments for patients with multi-drug resistant infections .

Background

India is home to 18% of the world's population, as well as a thriving biotech sector and global pharmaceutical production capacity. However, ethical concerns surfacing in 2013 have limited the numbers of clinical trials carried in India, such that it currently hosts less than 2% of clinical trials globally. Nevertheless, there is enormous potential for India to develop its clinical trial capacity, including in the area of antimicrobials.

Furthermore, AMR is a major global public health issue strongly impacting India. Treatment failure is increasingly common, and recently introduced AMR surveillance has identified alarming levels of resistance to commonly used treatments. A major contributor to the rise of AMR in India is the ready availability of over-the-counter antibiotics, emphasizing the need for enhanced antibiotic stewardship. Set against this potential for misuse, thousands of preventable deaths occur every year due to the lack of availability of antibiotics, stressing the additional importance of ensuring access to those in need.

GARDP and ICMR

GARDP is a non-profit partnership aiming to advance the development of new treatments for priority populations affected by the most pressing bacterial infections, with emphasis on drug-resistant infections caused by WHO priority pathogens. It aims to work with partners across the public and private sectors to accelerate late-stage development and sustainable implementation of treatments for priority infections and target populations, including children and neonates. The recently launched strategy of GARDP outlines ambitious plans to deliver five new treatments by 2025.

GARDP is partnering with ICMR to explore the potential to expand antibiotic clinical trial capacity in India. ICMR, the primary governmental body responsible for formulating, coordinating and promoting biomedical research in India, has had a focus on AMR since 2013. Important AMR initiatives have included a new AMR surveillance network, which has generated a clearer picture of AMR in the country, and a program to enhance antibiotic stewardship.

Regulatory context

A supportive regulatory framework is essential to promote both rigorous clinical assessment of safety and efficacy and the rapid availability of new antibiotics for infections for which there are limited or no treatment options. During the last 5 years, the Central Drugs Standard Control Organization (CDSCO), the key national regulatory body in India, has taken steps to improve transparency and consistency and to streamline regulatory processes. In March 2019, CDSCO introduced New Drugs and Clinical Trials

Rules, covering new drugs, investigational new drugs for human use, clinical trials, bioavailability and bioequivalence, and regulation of ethics committees. Equally important has been the role of ICMR in developing National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, to guide the work of ethics committees.

Clinical evidence requirements

Globally, regulatory authorities continue to discuss the most appropriate pathways for antibiotic development, particularly to take account of the challenges associated with drug development for antibiotic-resistant infections. The US Food and Drug Administration (FDA), European Medicines Agency (EMA) and Japanese Pharmaceuticals and Medical Devices Agency (PMDA) are in regular dialogue, share information, and have issued guidelines on streamlined regulatory pathways for antibiotics for patients with unmet need. These guidelines include discussion of the most appropriate trial design given the characteristics of products and their anticipated use, including treatment of drug-resistant infections. Streamlined pathways have been introduced when new products meet an important unmet medical need (and other key criteria).

Use of antibiotics in children and neonates presents a specific regulatory challenge. Often, new drugs are initially approved for use only in adults. The evidence required to secure approval for use in younger age groups varies according to circumstances, but regulatory agencies are encouraging drug developers to consider pediatric and neonatal use as early as possible and are requiring, as part of the approval process, the submission of specific pediatric development plans.

The design of antibiotic trials therefore needs careful thought and dialogue with regulatory agencies. They also present major practical challenges, for example in identification of causative pathogens, timely enrollment, underlying disease severity and proper considerations of antibiotic use prior to trial enrollment. These challenges are particularly acute for trials involving multidrug resistant pathogens and even more challenging when trying to design the right strategy for gaining regulatory approval for children and neonates.

Clinical trials in India

Recent changes have created a more attractive environment for clinical research in India, reducing the unnecessary evidential burden for product approvals in India and improving the efficiency of regulatory processes. Workshop participants identified a range of factors that need to be addressed to establish a stronger platform for antibiotic clinical trials in India:

Capacity: There is a need to develop the infrastructure in hospital facilities to carry out high-quality clinical studies and associated laboratory analyses.

Human resources: The skills of lead investigators and other health workers at trial sites needs to be assessed and developed as needed.

Ethics committee capacity: Local institutional ethics committees may not have the expertise or capacity to oversee clinical trials effectively, given their complexity.

Compensation: Developers remain concerned about the risks of compensation claims associated with suspected adverse events and the difficulties in carrying out causality assessments, particularly in neonates; however, the recently published regulatory guidelines address this challenge and few issues have arisen in recent years.

Sustainability: Clinical trial teams are frequently put together on a project-by-project basis, and without secure funding they are likely to be disbanded at the end of the clinical trial. More sustainable approaches are needed so that clinical trial centers can retain specialist staff and knowledge, reducing set-up time and costs for new clinical trials.

Local context: Patterns of drug resistance show great geographic heterogeneity. An understanding of local AMR patterns can reveal the most appropriate sites for clinical trials. Local input is also important for ensuring that trial protocols are appropriate for local clinical contexts. In this context, the surveillance work under ICMR's leadership is of critical importance.

Moving forward

The network of hospitals established by ICMR could provide the core of an infrastructure supporting clinical evaluation of new antibiotic treatments and products, including those developed in India. Potentially, capacity could be developed in steps, initially in small-scale studies addressing a high-priority challenge in a limited number of sites with the most advanced existing capacity, with additional sites being identified and supported to

develop their capacity and join the network over time. Such a network would support the generation of data required to meet Indian regulatory requirements, thereby accelerating the availability of new treatments in India. More generally, it could also advance the global development of much-needed new antibiotic treatments, particularly for neglected populations such as children and young infants. ICMR and DCGI would work to ensure there is clear regulatory guidance harmonized with global regulators, if possible, to conduct antibiotic regulatory trials thus ensuring that Indian sites can be included as part of global multi centric trials.

Action Items

- Solidify the collaboration between GARDP and ICMR for carrying out adult and pediatric antibiotic clinical trials in India via a Memorandum of Understanding that recognizes both organizations as end to end equal partners in this endeavor.
- Identify three clinical sites that could serve as the initial core for a future network of clinical trial sites involved in carrying out trials of antibiotics relevant to the AMR Indian landscape.
- Explore the possibility of conducting a small observational study at these three sites, to assess the suitability of those sites for enrolling patients for a clinical trial targeting carbapenem-resistant Enterobacterales.
- Once the sites are identified, supported and brought up to stringent regulatory standards, aim to test a high-impact asset targeting carbapenem-resistant Enterobacterales.

Agenda

Day 1	**Monday 25th November 2019**	
9:00- 9.30	**Registration**	
9:30-10:00 am	**Session 1:** **Introduction to workshop and Welcome remarks**	Professor Bhargava, Director General, ICMR Prof Ramanan Laxaminaryan Chairperson GARDP Board Dr V G Somani, DCGI
10:00-11:00 am	**Key notes** (20 minutes each) - *Public Health Driven Antibiotic Development* - *The role of ICMR in Enabling Antibiotic Clinical Development in India* - *The need to generate Evidence for the proper development and use of novel antimicrobial agents*	Dr Manica Balasegaram, GARDP Dr Kamini Walia, ICMR Dr. Seamus O'Brien, GARDP
11.00-11.15	**Tea break**	
11:15-1:00 pm	**Session 2: Regulatory Landscape for Antibiotic Development** *Clinical Development to meet the challenge of AMR in India: CDSCO Regulatory update (20 minutes)* *Understanding regulatory similarities and differences to enable global AMR trials: regulatory approaches to infections due to infrequently occurring organisms* *(20 minutes each speaker)* **Case study:** *Role of evidence and regulatory approvals in addressing challenges of clinical trials of drugs for resistant pathogens.*	**Chairpersons:** Dr VG Somani and Dr Gagandeep Kang Dr AK Pradhan, CDSCO Dr Sumathi Nambiar, FDA Dr Marco Cavaleri, EMA Dr. Junko Sato, PDMA Dr Larisa Singh, Medpace
1:00-2:00 pm	**Lunch**	
2 :00- 3 :00 pm	**Panel Discussion:** *Enabling a clinical trial for drug X in patients with serious Gram-negative bacterial infections and limited treatment options* *Open questions to the panel from participants*	**Moderators**: Dr Y K Gupta and Dr Sujith Chandy **Panelists :** Dr Pradhan, Dr Sumathi, Dr Cavaleri, Dr Sato, Dr Anand, Dr Jaideep Gogtay, Dr B K Rao
3 :00- 4 :30 pm	**Session 3: Neonatal and Paediatrics Antibiotic Development**	**Chairpersons:** Prof.R K Lodha

	A practical overview of the challenges in Paediatric Clinical trials for infectious diseases (10 minutes) *Regulatory overview in paediatrics Clinical development of antibiotics (10 minutes each)* - F*DA* - *EMA* - *PDMA* - *CDSCO* *Open questions to the panel from participants*	Dr.Ramesh Aggarwal, AIIMS Dr Sumathi Nambiar, FDA Dr Marco Cavaleri, EMA Dr Junko Sato, PDMA Dr AK Pradhan, CDSCO
4.30 -4.45 pm	**TEA BREAK**	
5.15 to 5.30 pm	**Summary and Recommendations of the day**	ICMR
Day 2 Tuesday 26th November 2019		
09:30-10:15 am	**Introduction to the day by chairpersons (15 minutes)** *ICMR network tertiary hospitals and its potential to become initial sites of a AMR clinical trial network to support to support national and international clinical trials*	**Chairpersons:** Dr Seamus Dr Kamini Walia, ICMR
10.15-10.30	**TEA Break**	
10:30-12;00 pm	**Session 4: Clinal Trial Site Requirements for Antibiotic Phase II & III Research (20 minutes each)** - *Case study presentation by PI / CRO on Antibiotic Phase III* - *Phase III experiences / capabilities clinical trials capacity in India* - GARDP aspirations - ICMR aspirations	Dr Ramasubramanian Dr Nilima A Kshirsagar Dr François Franceschi, GARDP Dr Kamini Walia, ICMR
12.00 to 01.00 pm	***Panel discussion:*** *Building the required capacity towards an Indian network for CT* - *Site requirements and capabilities* - *Site identification process* - *Capacity building needs*	**Moderators:** Dr Seamus O Brien and Dr Gagandeep Kang **Panelists :** Dr Francois F, Dr Kamini Walia, Dr Ramasubramanian, Dr Larisa Singh, , Dr Zakir Thomas and Dr B K Rao
1.00- 1.30 pm	**Recommendations of the meeting**	ICMR & GARDP
	Vote of Thanks	

List of participants

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