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Clinical trial networks for AMR research

How can we enhance interoperability between networks to improve the quality of clinical studies?

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Executive Summary

The importance and potential of collaboration in research, most notably with respect to clinical trials, has been clearly demonstrated by the COVID-19 pandemic. Despite initial progress in developing a combined response, it remains clear that fragmented and ad hoc approaches to clinical research will only compromise the quality and value of clinical evidence, reducing the speed to market of new, effective treatments.

Clinical trial networks are collaborative structures designed to support and enhance the efficiency and quality of clinical research through harmonisation, cooperation and resource sharing. These networks are usually established on a regional basis and sometimes as international programmes focused on single diseases. Wellcome aims to understand how collaboration between different regional antimicrobial resistance-focused clinical trial networks can be enhanced and optimised to further improve clinical research outcomes in the field.

A targeted consultation exercise was run in Spring 2020, involving a range of stakeholders from antimicrobial resistance- and broader infectious disease-focussed clinical trial networks. The aim of this consultation was to better identify the needs of and benefits to groups with regards to cross-network collaboration, identify the current barriers to integration, and begin discussions on potential solutions to address them.

The exercise identified four key areas where cross-network collaboration can help enhance and improve the efficiency and quality of clinical trials.

These were:

- Maximising the scale of collaborations to deliver actionable results
- Strengthening training and expertise sharing
- Improving cross-region regulatory science and streamlining regulatory processes
- Harmonising clinical trial data and enhancing sharing practices

Wellcome intends to further explore the above issues to bring clarity and greater understanding of the full impact of enhanced cross-network collaboration on clinical trials for antimicrobial resistance.

Management of the challenge to clinical research during the COVID-19 pandemic will provide rich lessons and insight into the potential of enhanced collaborations in clinical trials. We aim to help fill the remaining gaps where the absence of tools and systems facilitating cross-network functioning has limited progress.

A diverse range of actors are working to identify and address issues that impact the effectiveness of clinical trials based in a global setting; Wellcome will seek to galvanise the community and help develop workable solutions to overcome these issues alongside other actors.

Introduction

The COVID-19 pandemic has demonstrated the importance of large scale, international, scientific collaboration in the provision of solutions to global health issues.

The overwhelming consensus has indicated that the current public health crisis can only be ended through worldwide scientific partnerships, resulting in an extraordinarily rapid shift in the way clinical research is being conducted. We have seen what is possible when researchers, product developers, industry, funders, philanthropists and governments work together towards a common goal. An unprecedented number of cross-laboratory, cross-border, cross-industry and cross-sector partnerships have been developed, and all parties have embraced the sharing of resources, expertise, information and data. In the first 100 days following the initial, official reporting of COVID-19 cases, more than 600 relevant clinical trials had been registered and at the time of writing, at least 1,000 studies were enrolling participants.[1,2] In tandem, there has been support from approval panels and regulators, speeding up a range of processes, allowing patients to be enrolled in trials quicker and granting emergency use authorisations for early successes; all done without compromising on diligence.[3]

Despite the rapid mobilisation and clear common goal, there have been examples where a lack of cohesion between broader study teams has limited progress. Early indications suggest that in the absence of tools and flexible systems that facilitate greater levels of interconnection, competition has continued to have detrimental effects. Most notably, competition for patients has affected recruitment rates, leading to the achievement of fewer evaluable studies than potentially possible. It is vital that this new model of rapid and collaborative working and sharing continues, but to do so successfully, structures and initiatives that can both prioritise the most promising therapies and maximise cohesion must be identified and implemented.

Wellcome has advocated for the incorporation of more cohesive ways of working in the field of antimicrobial resistance (AMR) for many years, highlighting the potential of clinical trial networks to foster international collaboration and accelerate the clinical development process for antibiotics in 2016.[4] Clinical trial networks exist as organised groups of clinicians, researchers and their associated hospitals, sites and institutions, who share infrastructure and resources, enabling them to collaborate on multi-centre clinical trials. These networks have supported and increased the number of international studies run in a range of therapy areas, enhancing the quality and outcomes of clinical trials, which can be severely affected by several inefficient processes. Networks can ensure sustainability of structures and expertise, provide a base to help overcome the significant barriers to study start up, reduce trial costs and expedite study accrual.

Wellcome has recently established a clinical trial network in Asia to help mitigate inefficiencies in the funding, resourcing and conducting of clinical trials for AMR and infectious disease (ID) studies in low- and middle-income countries (LMICs). The network will strengthen and stabilise clinical research capabilities in the region through the provision of warm base benefits that will help accelerate trial start-up, shorten study timelines and lower costs.[4] A key goal of Wellcome's Asian Clinical Trial Network is the ability for it to collaborate effectively with other regional AMR and broader ID networks, allowing for wider geographic activity, while remaining financially sustainable and ensuring that the efforts of others are not unnecessarily duplicated.

Partnerships built between different regional networks have the potential to help increase the reach of research and future treatments to patients, enhance the capacity and expertise for clinical research in under-served regions, support the generation of larger sample sizes and provide wider access to shared intellectual infrastructures to conduct trials. These partnerships could further strengthen research capabilities and outputs, to more readily achieve global impact. With several regional AMR-focussed networks already in existence and others emerging, the concept of harmonisation and interoperability between them is highly relevant but understudied. There is a need to determine and detail what degree of collaboration can be achieved within the community, how best this can be put into practice and how groups can work together to ensure the optimal coordination of resources in the future. There is potential for the current limited interactions and mechanisms to extend beyond what has traditionally been done, in a similar way to the extensive sharing of data, resources and sensitive information seen during the COVID-19 pandemic.

This report highlights the outcomes of a targeted consultation exercise conducted as part of Wellcome's initial engagement with stakeholders to identify means to increase cross-network collaboration. Going forward, Wellcome is keen to gain the

commitment of stakeholders to support the development and implementation of collaborative initiatives and methods of functioning. We aim to work with others to ensure that barriers to collaboration are removed, so that another pandemic is not required to trigger such large scale, global cooperation in clinical research, but rather that this way of working becomes routine.

Methodology

As part of Wellcome's efforts to understand and overcome barriers to effective collaboration between clinical trial networks for AMR, the Drug-Resistant Infections Priority Programme ran a stakeholder mapping exercise to identify relevant networks. Active groups across a wide geographic range, undertaking studies in AMR and infectious diseases, primarily involving but not limited to antibiotics trials, were selected and invited to participate in activities. In addition, stakeholders from therapy areas where collaborations between network communities are well-established (e.g. oncology, HIV/AIDS, TB and malaria), were invited to join proceedings to provide learnings from the successful development of integrated structures between networks and working examples, which could be replicated within the target community.

Key representatives (network coordinators, administrators and principal investigators) from participating groups (see Error! Reference source not found.) were invited to share t heir perspectives and specific issues in individual, hour-long, semi-structured interviews, held between March and April 2020. Interview formats and lines of questioning were informed by a rapid review of the relevant literature and engagement with in-house clinical trials experts. The aims of this exercise were to:

- Establish the views and attitudes of the stakeholder community towards the potential for, and limitations of cross-network collaboration
- Gain insight of the types of collaborative partnerships already existing between networks
- Identify how greater levels of engagement can be facilitated to enhance the formation of new partnerships
- Understand stakeholders' knowledge and experience of existing resources that may support collaboration
- Identify the challenges and barriers to the process that can be solved collectively to enhance collaboration

Qualitative outcomes from this engagement were analysed and categorised, and are summarised anonymously, in the following sections. Where responses from stakeholders relate to information that is already in the public domain, these have been included, identified and attributed to an appropriate reference. Alongside these outcomes are ideas for potential solutions and suggested ways of working that will be taken forward and prioritised by Wellcome. In the process, we aim to gain the commitment of stakeholders to support and participate in the co-development of collaborative initiatives to address the most critical issues.

As part of wider activities in this space, Wellcome aims to fill the gap in understanding, and gain consensus within the AMR and broader ID clinical trial community, by engaging with and convening stakeholders to understand three key areas:

- The needs of and benefits to networks from wider collaboration
- The current barriers and how best to co-develop solutions to address them
- Lessons to be learned from the experiences and actions of clinical trial networks operating in other therapy areas (which may also unearth cross-area potential for collaboration, especially pertinent for AMR studies)

Consultation Outcomes

Interviews with participants were focused on gaining insight on three main topics:

- Current involvement in cross-network collaborations and form of partnerships
- Key barriers to integration and potential shared goals which could guide cross-network functioning
- Specific issues and best opportunities for aligning activities between networks

The responses provided by participants could be broadly categorised into four key themes:

1. Maximising the scale of collaborations to deliver actionable results
2. Strengthening training and expertise sharing
3. Improving cross-region regulatory science and streamlining regulatory processes
4. Harmonising clinical trial data and enhancing sharing practices

In discussions, participants not only discussed the challenges but were also encouraged to propose ideas for potential solutions. Future engagement with stakeholders will seek consensus on prioritisation of these outcomes to ensure collective action where it is needed most.

1. Maximising the scale of collaborations to deliver actionable results

To assess the type of cross-network collaborations stakeholders were engaged in and understand what the community could strive to achieve, participants were asked to outline their activities and the key issues restricting the formation of new partnerships. The responses provided illustrated a spectrum of collaborative relationships separated by degree of formality.

At the lower end of the scale are informal connections founded on general communication and information sharing between similar or co-sponsored groups and interactions maintained between investigators and former colleagues. One stakeholder highlighted as an example, the European and Developing Countries Clinical Trials Partnership (EDCTP), which encourages collaborations between its networks by including areas of harmonisation and the achievement of agreed joint milestones, in its funding conditions. At the more complex end of the scale are formal agreements on study collaborations, outlined in detail and usually developed with legal support. These include co-sponsorship agreements, material transfer agreements, and site- and trial-specific contracting. Participants reported that in recent years there has been an increasing tendency to favour trial-specific, rather than site-specific contracting when working with other groups. Trial-specific contracting allows for greater degrees of flexibility and is more conducive to the development and management of initial collaborative arrangements and integration of previously unconnected sites.

Middle-ground collaborative options using formal mechanisms that are either non-legally binding or require a limited amount of early commitment were also highlighted. Confidentiality or non-disclosure agreements were reported as useful instruments allowing for more open discussion between groups on study details and future plans, which many are reluctant to share outside of formal collaborations. This type of detailed initial engagement is a useful method of initiating links which may develop into more complexed partnerships in the future. In addition, the use of memorandums of understanding (MOUs) as a formal, but non-legally binding agreement allowing for intermittent involvement in the activities of collaborators was raised. Representatives from Antibacterial Resistance Leadership Group (ARLG) highlighted their use of MOUs in a series of agreements with partners including the Combatting Antibiotic Resistance in Europe (COMBACTE) network. ARLG signed an MOU with University Medical Center Utrecht (the managing entity of COMBACTE) in November 2018, to be each other's first point of contact when looking to incorporate sites outside of their own regions. This agreement was established to ensure coordination and streamlining between US and European clinical research efforts, reducing costs and avoiding duplication of efforts.[5] Despite the high level of support for the use of these mechanisms, issues with the protracted negotiation and development process of agreements and contracts were reported, highlighting the slow and cumbersome pathway to finalisation. Stakeholders conveyed the desire for a more simplified and streamlined legal negotiation processes to facilitate the ability to collaborate. This and whether a single contract negotiation process is sufficient for site access and site reimbursement, is especially relevant for drug developers wishing to utilise clinical trial networks to generate auditable and actionable Phase II and III data.

In therapy areas where cross-network relationships are well established, even more complicated structures exist including umbrella organisations responsible for facilitating and coordinating inter-network collaborations. The Office of HIV/AIDS Network Coordination (HANC) in the US is an example of this operating model, working directly with the Division of AIDS (DAIDS) funded HIV/AIDS clinical trials networks which focus on the development of improved HIV treatment and prevention strategies. HANC's role is to create a more integrated, collaborative and flexible research structure for the networks by supporting the science and operations through increased resource-sharing and coordinated cross-network activities.[6] The importance of forming collaborations beyond the specific clinical area of a network was also discussed by HANC. The organisation collaborates with the Tuberculosis Trials Consortium Community Research Advisors Group providing the opportunity to co-educate both research communities on how the two diseases are connected and coordinate engagement globally. This type of cross community engagement is highly relevant to the AMR and broader ID field due to wide interlinking with other disease areas.

Potential Solutions

There was consensus that a complex vision for the future should not be the starting point to enhance methods of collaborative working, but that there are straightforward options which could be prioritised and easily implemented now. The lack of visibility of related and similar networks across the world and limited opportunities for direct engagement with groups were reported as barriers to the process of building contacts and forming initial relationships with others. One network representative highlighted that good collaborative relationships take time to foster and are highly reliant on extensive and iterative trust building, which requires patience. For this reason, collaborations are often limited to groups with which there is an existing connection (e.g. between former colleagues or co-funded researchers). The consensus from stakeholders was that greater means to facilitate communications and dialogue between groups

which do not commonly interact would be welcome. Multi-stakeholder meetings were recommended as a good forum for groups with similar research goals to begin engaging with each other and establishing links with unconnected groups that can be fostered and developed into more complexed ways of working in the future.

It was also suggested that in the longer-term, the availability of a virtual AMR or ID specific communications platform or broadcasting hub could be an effective tool to facilitate wider interconnection of groups. Such a platform could provide facilities for the dissemination of information, resources to support global activities in a non-contractual manner and facilitate early study discussions. In addition, it may create a medium for the wider provision of experience, problem and solution sharing to support groups facing similar problems or issues, allowing for cooperation and joint resolution of issues across regions. The impact of COVID-19 has caused the world to reassess methods of communication, highlighting the utility of a digital communications platform. The vast array of technology, connectivity and streaming platforms that are currently available, suggest that sufficient technological infrastructure is already in place globally. However, how best a platform of this type can be organised and developed to be wide reaching, effective and sustainable is an important question for further discussion.

The potential for an AMR or ID specific clinical trial site registry was also raised. Stakeholders reported that a resource highlighting the capabilities, capacity and study experience of relevant sites would be widely welcomed to aid site selection for studies. One stakeholder mentioned the importance of site diversification in selection and the difficulties of integrating unfamiliar sites into studies. A sector specific system would require significant investment and continued funding to constantly update and maintain operations but may be supported by the pooling of stakeholder resources. During discussions, one stakeholder mentioned that the Global Health Network previously had plans to develop a similar resource which might present an opportunity for integration of programmes if the community decide that this should be a priority. Existing, more generalised platforms such as the Pan African Clinical Trials Registry funded by EDCTP and South African Medical Research Council (SAMRC), can be used as an example for further discussion. Wellcome is well placed and equipped to convene organisations and establish the relevant partnerships needed to drive this type of work forwards.

2. Strengthening training and expertise sharing

The potential positive impact of collaboration between networks on improving the provision of training in the clinical trials space was a consistently discussed topic during the consultation process. A wide range of aspects were highlighted by stakeholders; most notably, the benefits of training programmes to enhance trial site capabilities by strengthening the expertise of investigators and other site staff. This can be enhanced by the provision of support and mentorship to maintain the development of high-quality researchers for the future.

Some stakeholders reported their experiences of operating studies at sites with limited capabilities, collaborating with partners with inefficient processes, and working in regions and with institutions lacking adequate ethics and review board structures. These interactions negatively impacted the research outcomes with respect to timelines, quality and utility of data. As an example, one stakeholder highlighted an occasion where the running of a diagnostics study with partner sites was hindered by severe limitations in expertise due to inappropriate training of staff. In addition, participants were asked to detail the training and support provisions delivered by their networks to overcome these issues and for their thoughts on how working collaboratively may improve the delivery of training within the community.

Improvements to the quality and availability of tailored training courses for personnel at trial sites, especially in LMICs was highlighted as being of considerable importance to the clinical trials landscape and there was consensus that this can be facilitated through network collaboration. All participants involved in the consultation reported that their networks develop their own general training materials, run seminars and work directly with partner sites to improve standards. A range of training topics were discussed, including good clinical practice, human subject protection, enhancing site monitoring capabilities, quality assurance, and storage and retention of clinical research records. These areas were highlighted as key to improving site capabilities and efficiency, with emphasis on the positive impact of improved site monitoring on self-sufficiency and resource sustainability due to the reduced need for contracting CROs.

Alongside the wider dissemination of materials, the issue of limited accessibility to training in diverse regions due to language barriers was raised. Limitations in the availability and funding of translators can cause issues not only at an operational level (translation of consent forms and contracts from English to other languages and vice versa), but more importantly in accessibility to training offerings. Limitations in accessibility of programmes to non-English speakers in the absence of reliable translation services was highlighted as a key barrier to the free flow of information.

Beyond the provision of site-specific elements of training, the importance of mentorship and building wider expertise to maintain large communities of high-quality researchers for the future was highlighted. The focus should be at investigator level and this could be performed through the provision of long-term support for early-stage researchers to empower individuals and provide more directed support for protocol writing, grant and funding applications. Schemes which support personal development are of considerable value to researchers in low-resource settings, providing a means to follow progress and identify further learning and development needs, as well as creating routes within their groups for information and expertise to cascade more widely. One stakeholder highlighted a scheme that is run across integrated sites which facilitates mentoring through postdoctoral networks of linked research groups across the world. The scheme especially offers the support of mentors throughout funding calls, helping applicants to navigate the process from a practical perspective.

Potential Solutions

Training materials produced by networks independently are relevant and useful to the wider community, beyond individual networks. To reduce the replication of efforts and increase reach, stakeholders agreed that co-developing and sharing training programmes, workshops and seminars could be an effective option. This would be especially beneficial for groups and sites with limited resources, unable to invest in expensive activities such as quality management (quality control and quality assurance) training. Shared training resources could potentially be made available by the creation of a widely accessible platform to which parties can create, share, host and revise a wide range of educational content for use by a broad audience. It could function as a databank of knowledge through which information and expertise could be shared between sites and multiple groups and could form part of a wider integrated communications platform as previously mentioned. A resource of this type that could be made free to access aligns with Wellcome's approach to maximising the distribution, readership and impact of information to foster a richer research culture. In addition, seminars and live training sessions can be codeveloped between groups and held online via video conferencing with post-training electronic testing and certification, which will be especially useful for participants lacking the resources to attend international external courses.

Small-scale, educational resources of a similar type have been created in the past but were not deemed successful or sustainable due to a lack of awareness, limited accessibility and limited cross-community involvement. Indeed, there was limited knowledge among respondents of publicly available resources with AMR specific training materials. Stakeholders agreed that as a community, there should be a shared interest in improving the availability of training and an AMR or

ID specific central, collaborative resource would be of great value. It was also suggested that the Global Health Network is in the process of diversifying its AMR Hub to include AMR specific clinical programmes to serve a similar purpose. Instead of duplicating efforts, there may be scope to collaborate and codevelop an integrated platform specific for training resources for clinical studies in infectious diseases. Representatives from HANC also highlighted their positive experiences of working on the collaborative development of training programmes. For many years, HANC has contributed to the development of tools and resources for use by researchers, site staff and wider communities involved in HIV research and conducted evaluations to assess how to improve community participation in the research enterprise. In collaboration with DAIDS, HANC supports the development of a variety of training courses hosted on the DAIDS Learning Management Portal, and as part of efforts to work with other disease groups, in partnership with the TB trials consortium, HANC has developed a range of resources for community engagement around TB-HIV co infection.

In a similar way, agreements between groups to codevelop and cooperate on the translation of courses, programmes and schemes may help overcome language barriers in the provision of training globally. Representatives from ARLG suggested that a series of reciprocal agreements with local partners through MOUs to share the load in developing materials and supporting translation into required languages could help enhance accessibility. Further commitment from other stakeholders can be sought to build a multi-language training network with a broad global reach.

Cooperation and collaboration between groups can be used to help develop mechanisms to provide more directed and sustained development opportunities for early-stage researchers, especially those in resource limited settings. The mentoring schemes that were highlighted in examples by stakeholders can potentially be run across networks and better integration between groups could allow for the development of secondment and exchange schemes. Practical skills and expertise can be acquired by participants first-hand through these mechanisms, and subsequently disseminated further within their home institutions upon return.

Enhancement of training provisions, both at site and investigator level, appears to be the area most amenable to benefit from collaborative approaches. Stakeholders agreed that as a community, more can be done to stimulate the joint production of programmes, running of joint events, sharing of resources and dissemination of materials using online systems. A key point highlighted by groups was the importance of making these resources freely and publicly available.

3. Improving cross-region regulatory science and streamlining regulatory processes

There was widespread feeling among stakeholders that the complex and differing regulatory requirements between countries, regions and jurisdictions are a fundamental obstacle to international collaborations.

The most commonly discussed issue was the wide variations in regulatory guidelines and the impact of the transient and continually evolving regulatory landscape. The associated challenge of keeping track of changes was mentioned, alongside the increasing layers of intricacy and bureaucracy that have become evident in recent years, and the fact that elements can even change during a trial, further impacting delivery and increasing the need for regulatory support. One stakeholder highlighted the impact that the introduction of the European General Data Protection Regulation (GDPR) has made on consent and data processing for clinical studies and the need for access to expert knowledge to help ensure compliance.

Limited knowledge of the details and country-specific nuances in regulatory and administrative processes for clinical trials was highlighted, with differences in the requirements for endpoint selection and data review policies between EMA and FDA used as an example. In addition, the wide variety of processes and issues with different levels of regulatory standards, particularly in LMICs were mentioned. International, multi-site trials require multiple institutional review board (IRB) approvals and geographic variations in structure, standards, regulations on sample processing and speed of review, were mentioned as factors negatively affecting clinical research collaborations. These issues often impact study schedules with one stakeholder reporting that extensive review times have caused delays in implementing grants and on occasion have led to grants expiring prior to trial initiation. Variations in regulatory and ethical guidelines across regions also limit the ability of investigators to implement the same trial protocol across all study sites. This was highlighted as a key issue by the government funded clinical trial networks, as it conflicts with specific requirements from their funders. For these groups, the use of standardised protocols across all sites, irrespective of region is stipulated by funders, making involvement in cross border studies challenging.

Requirements for standardisation are further impacted by regional variations in standards of care (SoC) which were also reported as barriers to conducting international studies. In some regions, the SoC is frequently inappropriate, not defined or in areas with extremely limited resources, non-existent. Variability in standards of care across studies severely impacts the comparability of outcomes and the quality of the evidence produced. The issue can be further compounded by restrictions on the import and export of medicinal products, medical devices, samples and specimens across borders and the expense of making stocks available at each individual site despite there being no guarantee of enrolling patients at all sites. Stakeholders involved in HIV/AIDS research reported that SoC selection in multi-national studies was a controversial issue in the field during the 1990s, highlighted by the failure to provide HIV-positive control groups with any treatment where there was no registered standard of care.[7] Representatives reported that large scale, coordinated engagement with the research community and research ethics committees (RECs) was necessary to help drive the redevelopment of ethics guidelines. In addition, advocacy for post-trial access to approved products for trial participants and local community stakeholders was a key part of the redevelopment process and has been included in good participatory guidelines for HIV prevention trials since. Learnings from this process may be used to help facilitate similar action to support AMR research.

Stakeholders in the field of international cancer therapy also described the impact of conducting studies in low-resource settings and lessons learned from working with local drug regulatory agencies and ministries of health. In one example, significant delays to study timelines and outcomes arose from the need to develop a framework to discuss bioethical considerations of cancer therapies as review processes were largely based on HIV prevention and treatment studies. To address these problems, the organisation invested in capacity building and training activities to strengthen local regulatory ethics committees and advance regulatory science for these studies, which required very different risk-benefit considerations for approval. This example is important when considering clinical trials for host directed therapies for infectious diseases.

Potential Solutions

Overall there was consensus among stakeholders that the variability of regulations between countries and limitations in access to key regulatory expertise are barriers to running cross-regional studies. Effective initiatives to manage or potentially even decrease the regulatory burden surrounding clinical trials would help facilitate international studies. The availability of a streamlined mechanism to improve understanding and share access to specific regional regulatory knowledge would be particularly useful to the research community.

Potential solutions that arose from discussions included an extension to the potential virtual communications platform mentioned previously that would allow for discussion, experience sharing and access to advice from regional regulatory experts from other networks. How this could work and the practicalities of this are important elements for further

discussion. It may be that recruitment of external experts is required to supplement the existing expertise from within networks interested in contributing to such an initiative. Alongside this, it was agreed that the availability of a resource outlining multi-aspect regulatory and ethical guidelines in different countries and regions, highlighting how different regulatory bodies work and specific requirements to achieve for approval would be beneficial. Antibiotics studies could be further supported by resources providing information on international standards of care across countries. A resource of this type could be co-developed by different networks, building out from available prescribing guidelines in multiple settings and potentially organised by syndrome.

Evidence has recently emerged from research on the geographic shift in clinical trials for antibiotics that reduces concerns around the generalisability of data from different regions.[8] As a result, there is likely to be a rapid increase in the number of studies conducted in LMIC settings in the future, increasing demands on fragile IRB and REC structures in countries with limited resources. The model of regulatory system strengthening, and capacity building highlighted above can be replicated by groups of networks, collectively investing in regions to help accelerate and improve local approval processes. Capacity building and training in these settings will improve clinical trials oversight and ultimately medical management. At the same time, this will increase the need to streamline and simplify the number of review processes necessary for multi-country studies. This could be achieved by centralisation through which a single body would assume responsibility for an entire trial, with individual, local IRBs responsible for assuring compliance with local laws. This may be beyond the scope of commitment of involved networks but is an area that the group can advocate for. In addition, the streamlining of IRB approval would be highly beneficial for industry sponsored studies run within clinical trial networks. The question of whether study approval can be provided once across a network for all sites, remains a key issue that could be resolved by a modified and accelerated approval process.

With respect to generating auditable and actionable data for Phase II and III clinical studies, network collaborations could help mitigate the costs and facilitate the management of sponsor oversight. There is potential for data auditing services to be shared across collaborating networks, with the employment of targeted risk-based monitoring strategies which may prove to be more cost effective. However, this would need to be managed strictly to ensure that the delegation of duties is clearly documented and there is no ambiguity which could lead to poor adherence with regulatory requirements.

4. Harmonising clinical trial data and enhancing sharing practices

When asked to highlight what, if any, data related issues have impacted the ability to collaborate with other groups in the past, the responses of stakeholders were wide ranging. Reports included confusion with partners in distinguishing the intricacies between data sharing and data ownership, disputes over publication rights, confidentiality breaches and limited availability of data sharing and harmonisation systems.

Difficulties in developing agreements for the usage and sharing of data were described as key issues in data management, especially in collaborations between academic institutions and industry. Conflicting opinions regarding publication of outcomes and decisions on publication rights were highlighted especially by the government funded networks who are not only encouraged but, in some cases, mandated to publish studies as soon as data are available. None of the participants reported that they demand ownership of data but there were reports of experiences of disputes with collaborators regarding terms of data ownership, sharing and re-use, requiring legal negotiation that was inconvenient and costly. One stakeholder discussed misunderstandings between the terms data sharing and data ownership as a common hindrance to the development of agreements. It was highlighted that although possible to navigate, the issue is one that is tedious and requires engagement with legal representatives. Alongside this, the impact of regulations and GDPR on data sharing processes, especially on the restriction of existing informed consent which does not expressly cover the sharing and reuse of trial datasets, was highlighted by stakeholders. In response to this, it was suggested that support could be given to researchers when obtaining consent to ensure all agreements fully detail conditions of immediate data usage and the potential for future sharing or re-use of data from studies.

When asked about their familiarity with and use of any clinical data sharing platforms, there were mixed responses from stakeholders. Knowledge of commercial platforms was reported but experience of working with these was relatively limited. Only one infectious disease specific data sharing platform was directly mentioned; a resource for sharing TB clinical trial data, developed by the Critical Path Institute in partnership with the Special Programme for Research and Training in Tropical Diseases (TDR), the TB Alliance, and St. George's, University of London.[9] In discussions that were more focussed on advancing and encouraging data sharing more widely within the community, stakeholders highlighted potential difficulties due to the vast variability of data standards. Inconsistencies in data capture, preparation, processing and storage, which make combining data from multiple sources incredibly difficult were highlighted by stakeholders and there was agreement on the need for an alignment of data standards, supported by appropriate training and coordination within the community.

Potential Solutions

There was clear consensus that it is important for the community to encourage and advocate for improved availability, publication and sharing of data and that there should be a commitment to sharing deidentified individual patient data more widely. The Data and Specimen Hub (DASH) run by the US National Institute of Child Health and Human Development (NICHD) was highlighted as a good example of a centralised platform that supports this. In addition, the Specimen Repository was mentioned as a resource developed in collaboration between several HIV-focussed clinical trial networks that makes protocols and specimens available to researchers conducting new studies. Data and protocol sharing are vital to improve and inform the design of future trials. Alongside the development of an integrated network communications platform, data sharing will help prevent the unnecessary duplication of efforts in clinical research while promoting necessary replication of studies when needed, for example in special populations. It was recognised that efforts to harmonise data standards across such a broad field would be an incredibly resource intensive activity but could start with a small group of networks initiating an agreement to define, develop and maintain standards that can be approved for others to connect with and implement in the future. How this type of initiative can be initiated and the identification of willing partners to collaborate in developing standardised processes and data collection practises will be the next important steps.

Networks can support the improvement of data sharing from studies by more frequently making use of blanket agreements during study development to cover data handling, reporting and publishing between groups. In the process it will be important to better outline data ownership and data sharing practices to be implemented and ensure informed consent for future use. The clinical trial community will also benefit from advocating more broadly on the importance of publishing data. There is a need for increased engagement with and support and understanding from publishers to help drive this, especially with regards to recognising the utility of smaller datasets as the best available early evidence in clinical research.

Finally, the visibility and availability of clinical trial data sharing platforms and repositories can be enhanced to facilitate their use within the AMR and broader ID communities. It will be important to assess the needs of the community for the development of an infectious disease specific resource or whether currently available disease agnostic platforms will be sufficient to meet requirements. Any evaluation of platform suitability can be built into the exploration process of data standard harmonisation with

groups, and knowledge and experience shared more widely through communications platforms. Principles of ‘FAIR data’ should be implemented to ensure data are findable, accessible, interoperable, and reusable.[10] Wellcome is already well positioned to support this, with active workstreams in collaboration with partners assessing how best to support and encourage clinical trial data sharing in other fields.[11] Familiarity with the related issues and needs between different research communities will help in the prioritisation of efforts.

Takeaways and Next Steps

The clinical trial landscape for new antibiotics and treatment strategies to address antimicrobial resistance is burdened with inefficiencies which slow down the registration and commercialisation of products. These are circumstances which are reflective of the broader situation for clinical investigations for infectious disease interventions. Clinical trial networks are collaborative structures which can enhance the efficiency and quality of trials, through cooperation and resource sharing. Even greater resource-, time- and cost-saving efficiencies may be achieved through further collaboration between individual regional AMR- and ID-focussed networks, creating a more streamlined development process for antibiotics, improved access to leading global clinical expertise and greater resource, data and protocol sharing. Despite its relevance and importance in this space, the concept of harmonisation and interoperability between networks is underutilised and consensus on how best to put it into practice is currently unavailable. However, recent examples of the emergency response during the COVID-19 pandemic are highly instructive. For example, the RECOVERY trial has demonstrated efficiencies that are achievable through network structure, clear principles and systems for data sharing, and streamlining of clinical trial design through the use of adaptable platform protocols.[12]

Wellcome aims to address the gap related to enduring clinical trial networks by convening relevant stakeholders to identify the full range of potential benefits of enhanced collaboration, understand the needs of the community, identify existing barriers and co-develop long-lasting solutions to address them. In addition, lessons can be learned from the experiences and actions of clinical trial networks operating during the COVID-19 pandemic as well as those focused on other therapy areas. Engagement with groups from other areas has the added potential of identifying cross-area potential for collaboration, especially pertinent for AMR studies due to the significant interplay with cancer, acute critical care and surgical interventions among others.

This report outlines the outcomes of the initial steps of this process, a consultation exercise run in Spring 2020 involving coordinators, administrators and principal investigators from AMR- and ID-focussed clinical trial networks. The exercise yielded four key themes which encapsulate the breadth of issues that community members feel play a role in limiting collaborations. These are:

1. **Maximising the scale of collaborations to deliver actionable results**

   Small scale collaborations exist within the community however there is scope for even greater degrees of formality within partnerships. Increasing the visibility of networks and creation of more opportunities for groups to interact and initiate conversations are needed to enhance collaboration. A virtual communications platform to facilitate interactions may be an effective way to do this.

2. **Strengthening training and expertise sharing**

   Limitations in the availability and quality of training resources affect the quality of trial sites and research outcomes. The co-development and sharing of training programmes, knowledge and expertise between networks can help improve the availability and reach of resources within the community, especially in LMICs.

3. **Improving cross-region regulatory science and streamlining regulatory processes**

   The intricacies and variations of regulatory requirements and limitations of access to cross-region regulatory expertise, significantly impacts international collaborations. Inter-network co-operation and co-development of resources outlining the regulatory and ethical requirements in different regions can help support the running of multi-national studies.

4. **Harmonising clinical trial data and enhancing sharing practices**

   Improving mechanisms to make data accessible and re-usable is vital to enhance clinical research. The clinical trial network community can work collaboratively to develop and optimise systems to improve data standards and increase and encourage data sharing.

The activities that have contributed to the development of this report are intended as a starting point to stimulate discussion within the community and identify early evidence to inform action. The valuable insights into the issues facing groups and how these may be solved will be used to inform further discussions that will yield additional opinions. In combination, there is huge potential to learn lessons from both the successes and shortcomings of the rapid launch of activities related to COVID-19. Wellcome is committed to galvanising and supporting the community in the identification and

development of solutions to the issues outlined. Future engagement with stakeholders will seek consensus on prioritisation of these outcomes and develop a forward path to the design and implementation of activities and initiatives to overcome the key barriers to network collaboration.

The clinical research community needs to be forward-thinking in order to simplify, harmonise, and improve the efficiency of multinational studies. This will not happen organically and due to its complexities, this change will require more haste and less speed. Wellcome's plans are vital to initiating the formal conversations which have been lacking until now and in partnership with others, setting out the ideal way forward.

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Appendix

Participant list for stakeholder interviews:

Jameela Nikolich, Heather Cross and Chris Beard – Antibacterial Resistance Leadership Group (ARLG)

Kathy Brickell – Irish Critical Care Clinical Trials Network (ICCCTN)

Mags Thomason – PANDORA

Russell Campbell and Jeffrey Schouten – Office of HIV/AIDS Network Coordination (HANC)

Thomas Uldrick, Mac Cheever and Judy Kaiser – Cancer Immunotherapy Trials Network (CITN)

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Support for concept and outcomes development:

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Wellcome Trust Asian Clinical Trial Network

Herman Goossens – European Clinical Research Alliance on Infectious Diseases (ECRAID)

John Rex – F2G, Ltd

Mike Sharland – PENTA Child Health Research

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