The Drugs for Neglected Diseases initiative (DNDi's) response to 'Public consultation related to the WHA 75.8: Strengthening clinical trials to provide high-quality evidence on health interventions and to improve research quality and coordination'

Question	Feedback
The clinical trials ecosystem is the sum of all elements required to fund, prioritize, design, conduct, monitor and report scientifically and ethically appropriate, well-designed, and well implemented clinical trials as well as features necessary for oversight and coordination". Does the above description capture critical elements of the clinical trials ecosystem?	• Suggest adding a mechanism to coordinate research response with policy and/or guideline change (clarity on relationships between regulatory approval and policy change, facilitation – transparency in process) • Suggest adding the word 'quality' to the description. E.g. "well-implemented, well-designed, high **quality** clinical trials"
Are you aware of existing initiatives besides ICH related to strengthening global, regional, or national ecosystem	• ICMRA was useful during COVID as a forum for regulators to coordinate COVID-19 related reviews (COVID-19 | International Coalition of Medicines Regulatory Authorities (ICMRA)) - it become more systematic in the case of PHEICs for example and contributes to a coordinated regulatory ecosystem – all clinical research platforms (EDCTP-funded, DNDI disease specific, HIV networks, ANTICOV, PANTHER[1] (soon), and of course all TDR training) include a significant component of HR training, GCP training, lab training – little is done on statistics There are not enough Phase 1 centres in LMICs nor CDMOs to prepare, label, ship clinical trials medication. Insurance remains a barrier in some countries. • Harvard multi-regional clinical trials Home - The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (mrctcenter.org) • Transcelerate – especially re templates for protocols, SAPs and CSRs. Could be encouraged or adapted for use in LMICs. .
Are there adequate CT network initiatives currently or more or less needed	Overall, there is scope for additional CT network development – both new networks and better connectivity between those that exist already. The DNDI Human African Trypanosomiasis, Leishmaniasis (LEAP) Platforms and Chagas Clinical Trial platforms are good examples of well-coordinated disease specific CT networks. For pandemic preparedness, PANTHER aims at leveraging what exists – strengthen where needed – coordinate and promote

[1] **PANdemic preparedness for Health and Emerging infections' Response (PANTHER)[1]** -A sustainable & collaborative clinical research platform - linking Europe and Africa - for preparedness and rapid pandemic response. The initiative aims to develop, implement and sustain a "ready to use" living clinical research platform which integrates research capacity in clinical care. The platform will provide the human and technical infrastructure to timely address LMICs medical research questions through a network of equipped and trained researchers combining experienced African research centres with healthcare sites both in key population centres and more remote locations.

	knowledge sharing – prepare with stakeholders (TPPs, protocols, drug review) and be ready to rapidly implement. There are several networks dedicated to AMR (e.g. ECRAID) or paediatric development (e.g. PENTA network). However there is still a need to extend these networks to regions with the highest burden of AMR in an effort to conduct trials in these regions but also to generate relevant evidence of effectiveness in these regions.
What additional steps can be taken to facilitate rapid implementation of agreed trial protocols during pandemics and epidemics	• Define target medicine profiles early. These should include a view on minimum efficacy, minimum safety, comparators to be used. • Develop Master protocols which are pre-approved via joint mechanisms • Ensure that there is a pre-approved funding envelope to start activities up to enrolment of a set N of patients– • joint IRB/EC/NRA reviews with country endorsement and attached import license agreement – • Ensure sites are identified and "ready-to-go". These sites should be allied with trial networks to ensure that they have an active research portfolio in 'peace time' as well as during a pandemic – to retain staff and skills. This last point is critical. For regions with high burden of for example NTDS or AMR, NTD or antibiotic and related clinical trials could be the ideal peace time research activity that keeps these systems warm, generate data that is useful to these regions and in the end improve quality of care and patient safety. • On the drug development side: fund Phase I program in the target population to understand PK/PD before phase 2 – develop manufacturing agreements with identified license holders where feasible to agree on access conditions • Promote national or regional mechanisms for the prioritization of protocols. Several sponsors approaching the same sites/institutions will slow down approval and implementation and could lead to less important research being conducted. • Establish patient panels/community advisory groups ready to review and contribute to the development of protocols to ensure patient-focused outcomes.
What do you consider to be "the respective roles of the WHO Secretariat, Member States and non-State actors, best practices and other measures to strengthen the global clinical trial ecosystem, taking into account relevant initiatives where appropriate"?	• Member States should define R&D priorities for their population and selectively fund and support aligned research. • WHO Secretariat could coordinate global stakeholders consultation on treatment protocol guidelines, agreements on endpoints and publish (as was done eg for Sleeping Sickness) • In the case of pandemic WHO should play a coordination role between partners to ensure that rapid collection, analysis and dissemination of efficacy and safety signals can be shared with the research community for adaptation if needed –

	• WHO would also coordinate the scientific prioritsiation of compounds to be tested in the case of a pandemic – • R&D Non state actors can support advocacy for disease-specific research – will conduct R&D, support regulatory and policy change and conduct implementation research. • Non-state actors, supported by WHO secretariat can develop data standards for diseases of interest to allow collection of core disease data – facilitating data sharing and re-use.
Focus on preventing underpowered poorly designed studies	• Solid statistical review of protocols submitted for funding should be prioritised by ethics committees/national regulatory authorities as well as funders. Adequate training of approving bodies in the assessment study designs being fit for purpose. • Capacity building in new statistical approaches such as the use of Bayesian statistics could be beneficial. This could be delivered through the endorsement of approaches, publications on potential approaches. • Underpowered is not the same as poorly designed – a study could be well designed but insufficiently powered due to insufficient financial resources • FDA guidance for industry provides a roadmap for drug developers on the endpoints and power required for registration. WHO could produce disease guidance for minimum expectations on trial designs – to be used by member states during assessment of trials for approval. • Investing in development and funding of data standards could allow several countries to pool their data without having each (if they sponsor for example) to analyse them for a global analysis –
What are the best practices in reducing research waste (waste: any practice that does not allow outcomes of research to contribute to science or public health, including poorly designed, implemented or reported research studies), and what are the roles of WHO, Member States and non-State actors in implementing such best practices?	• National authorities, especially in the context of a pandemic, to set up review committees to prioritise research to be conducted in publicly-funded health systems. • Encourage national research ethics committee coordination to set agreed standards. • Encourage registration of all trials at a national level to have a full picture of research being conducted - and to allow recommendation of termination of research which is not adding value.
What measures are needed (legal, technical, other) to ensure that fair and transparent processes are in place to enable access to and reuse of clinical trial datasets in a manner that is appropriate for diverse settings?	• Ruling more data sharing as a pre-requisite for funding and defining timing, content and process. • Developing (or advocate for the development of) an appropriate standard for anonymization of data prior to sharing (not relying on GDPR) since this adds a significant barrier and is hampering data sharing. • Fund SDTM (e.g. CDISC) data standards so that pooling / integration of data between several studies is set-up before actually needed.

What do you consider to be measures that can be taken to better utilize digitization and move towards paperless approaches to clinical trials whilst safeguarding subject protections and data quality, measures that are suitable for countries of varying income levels around the world?	• Support to field-adapted digital technologies • Review of interpretation of GCP as it may be unnecessarily overinterpreted (incl the need for paper-proofs) – involve regulators in this process – make sure LMICs are part of the consultation • Clarify what the expected standard is for validation of electronic signatures and systems, since the often-used FDA 21 CRF Part 11 standard is overly onerous for LMICs. • Support or endorse open-source electronic data capture systems. • Support or endorse open-source electronic case report forms and electronic site and master trial files.
What measures can be taken, and by whom, to address the insufficient representation of specific population segments in clinical trials (LMIC populations, pregnant and lactating women, neonates, children, the elderly and the immunocompromised)?	• Guideline in the case of "global trials" in support of the development and validation of statistical approaches (e.g hierarchical models) to allow interpretation of results for populations of interest (geography, gender, age, disaggregated ...) – including pre-defined sample size justification • Regulators and policy-makers should engage in a dialogue that helps developers to design studies according to agreed (disease-specific) principles such as: e.g : required minimum effect size, required minimum sample size , management of heterogeneity . Not all studies will be of N=40,000 as seen during COVID ... But conversely how much would be needed for policy change and what do countries need to accept results as indicative enough for recommendation • Support the collection of real-world data post-marketing which can be used for label extension in special populations. • Encourage more use of modelling, and work to strengthen the used of big data to produce models, to avoid (or reduce) the need to study all special populations and speed access. E.g. approval in children with fewer children exposed. • Encourage the conduct of FEED and EFD (reprotox) studies early in drug development so as to enable participation of Women of child bearing potential and other atrisk populations early on • Encourage and incentivise paediatric development in parallel with adult indications to enable proper use in this age group • Encourage and incentivise studies in special populations not included in the pivotal studies, particularly those that are relevant to the indication.
What measures can promote clinical trials that address unmet needs in populations that have been neglected or underserved (NTD, rare diseases, WHO priority list of antibiotic-resistant bacteria and Blueprint priority list)?	• Once those diseases are identified as priorities, ensure that guidance is available for developers (and funders) so that the end product has reasonable probability of being considered for policy change if results are aligned with guidance. • Support initiatives to better define how to conduct research in children, young women, elderly.

	• Support dedicated funding mechanisms as well as an emergency fund. • Incentives – e.g. the FDA priority review scheme has had some impact, although still lacks access provisions . Could explore the potential of a scheme where there is priority review for essential medicines list adoption or pre-qualification on the basis of unmet need/priority. • Recent WHO priority pathogens list for fungal diseases is a good example – provides evidence for sponsors to advocate for trials for priority diseases, both internally and with funders and other stakeholders.
What measures can be taken, and by whom, to ensure evidence generated from clinical trials is considered higher quality from the clinical guidelines' perspective?	• Guidelines for the development of DTV for NTDs or pandemic-prone disease are scarce. Developing those disease specific guidelines (in the inter-crisis period) with regulators and policy makers would better support adoption – • TPPs are part of the plan and must be developed with the communities and involved partners so that the end product can be easily deployed for the target community - Posting those guidelines should support industry's engagement. • Define criteria for membership to Guidelines Development Groups - discussions should be made public • Could produce or endorse guidance on specific quality tolerances/standards for clinical trial data. Data that meet that standard to be prioritized for guidelines. This guidance should be different from that of stringent regulatory authorities – to make it appropriate for lower-resource settings.
How can research funding agencies work more effectively together, particularly during epidemics and pandemics? And how best can funding address the inequities in current resource allocations to LIC and LMICs?	• Ensure representation of LMCs membership in selection of projects • Allow LMICs researchers to receive funds – possibly identify Regional Centres of Excellence / Hubs as eligible recipients • Start with a case study – e.g. monkeypox or Ebola in Uganda
Other than ICH, what critical initiatives relate to the resolution and may already have articulated best practices and clinical trials ecosystems, as framed by the resolution? For example, what is your perspective on clinical trials and the CIOMS Working Group report on clinical research in resource-limited settings? What is your view of the Good Clinical Trials Collaborative guidance?	• Full support to the CIOMS working group report – highlights many of the LRS challenges and needs. • Full support for the Good Clinical Trials collaborative guidance. • These above guidance apply the broad ICH principles, and yet embody the spirit of the Helsinki declaration, making them better suited for application in low resource settings. However, data generated from trials utilizing these standards is not always deemed satisfactory for regulatory submissions by (SRAs).
Given very limited resources, what should be the key priority for improving the ICTRP database, Search Portal and Registry Network to	• Easy stream-lined processes for registration and upload of trial data are required.

adequately support the clinical trials ecosystem? How can quality of registration data best be improved at both the source registry level and at the ICTRP level to support the aims of the resolution?	
What measures can be taken to improve visualizations in the observatory?	No opinion
How can the ecosystem lead to efficient adaptation and deployment of capacities during PHEIC? Please offer examples of best practices and lessons learned. What do you consider best practices of expedited procedures for rapidly implementing clinical trials in PHEIC that meet regulatory and ethics oversight?	African Vaccine Regulatory Forum (AVAREF)- a network of African regulatory authorities and ethics committee which was formed with the aim to harmonize regulatory processes and expedite timelines for approval of clinical trial applications. Networks like this can facilitate quicker approvals of clinical trials and access to health tools during PHEIC.
If you have any comments, lessons learned, gaps or bottlenecks relating to the clinical trials ecosystem you would like to share, which are not addressed in the previous questions, please provide them here.	• Promotion of combined regulatory and ethics review processes. • Strengthening of regulators and promoting trans-national regulatory interactivity (especially in Africa) to facilitate timely and appropriate review. • Investing in data management systems in LMICs (example: Data Management and Biostatistics Centre created by DNDi) • Links must be made to resolution WHA 72.8 'Improving the transparency of markets for medicines, vaccines and other health products', adopted at the WHA 2019- which urges Member States to take necessary steps to mandate public availability of detailed clinical trial cost data and support dissemination of and enhanced availability of '….costs from human subject clinical trials….' , particularly in instances where these trials were publicly funded. One way of mandating disclosure of clinical trials costs is for governments/donors to attach conditions on price transparency and access to the health tools • Development of best practices for countries on how to ensure access and benefit sharing principles are implemented • Development of recommendations/principles, to facilitate access to comparator drug, tests, vaccine or assays needed for clinical trials in order to develop or compare technologies.