Briefing Document
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MSF Comments on the Clinical Trial Resolution at the 75th World Health Assembly

At the 75th World Health Assembly (WHA) in May 2022 member states will discuss and debate a resolution on clinical trials. Médecins Sans Frontières/Doctors Without Borders (MSF) recommends the following actions to member states to strengthen the resolution, so it can better serve public health needs:

1. **Ensure that the scope of the resolution is applicable to all clinical trials related to all medical technologies and not only to vaccines; guarantee that it covers clinical trials for all health needs and not only for health interventions addressing pandemics**
2. **Include full transparency requirements, such as sharing of protocols, timely publication of data and public disclosure of research and development (R&D) costs, including the costs of clinical trials, particularly when public funds are assigned to the research**
3. **Take into consideration the need for diversity of populations enrolled in clinical trials, as appropriate**
4. **Safeguard unhindered access to comparator drugs, diagnostics and vaccines needed for research and/or bioequivalence purposes**
5. **Embed access and benefit-sharing principles and conditions in clinical trial management and governance**

Background

The United Kingdom and Argentina are tabling a resolution on clinical trials at the upcoming 75th World Health Assembly. The zero draft, leaked by several NGOs, articulates important features to be incorporated in clinical trial policies and practices, including: a) enhancing clinical trial capacity in developing and low- and middle-income countries (LMICs); b) enhancing collaboration and coordination to avoid duplication; c) streamlining ethical standards and governance of sharing of data among regulators; d) ensuring sufficient size and appropriate design of clinical trials, and encouraging collaboration with affected communities in how they are conducted.[1]

MSF broadly supports these features and principles articulated in the zero draft. However, there are five key aspects at the core of clinical trials that member states should take up to ensure sufficient protection of public health needs, equitable access to health technologies resulting from trials, transparency and sharing of key data.

1. *Scope of the resolution*

The draft resolution brings important principles and recommendations for improving the capability of clinical trials, strengthening international collaboration, timely publication of data and improving standards.

MSF believes that the draft resolution should contain specific commitments for prospective registration of clinical trials and their protocols, as well as the publication of their results and data. The recommendations and policy guidance put forward in the resolution should not only cover the generation of evidence for all health technologies, but also cover issues related to the cost of generating this evidence.

While the overall text of the zero draft discusses clinical trials in general, operative paragraph 9 (OP9) restricts the draft's scope to COVID vaccines only. This contradicts the rest of the draft which does not contain any restrictions on disease area and the type of technology.

The COVID pandemic holds important lessons concerning the fragmentation of clinical trial planning, coordination and collaboration. Large scale internationally coordinated trials such as WHO´s Solidarity Trial are examples that can be emulated in the future. While these lessons and experiences can be a good reference, member states should not limit the scope of this resolution to COVID vaccines alone. Instead, they should take this as an opportunity to articulate clinical trial policies for all medical technologies applicable in both pandemic and non-pandemic situations.

2. *Timely publication and full transparency of clinical trial data and costs*

Recalling the WHO joint statement on clinical trial transparency, all clinical trials should be prospectively registered in a register listed in the WHO International Clinical Trials Registry Network; study protocols should also be made publicly available as soon as ethical clearance has been obtained.[2] Upon study completion, results should be disclosed on a clinical trial registry within 12 months, and published in an open access journal within 24 months.

MSF recalls resolution WHA 72.8 on "improving the transparency of markets for medicines, vaccines and other health products" which explicitly urges member states, through their national legislative framework, to take steps to enhance dissemination and access to the cost of clinical trials.[a]

According to the Report of the UN High Level Panel on Access to Medicines, there are significant differences between the cost estimates of R&D for new drugs, as there are few studies and the information available is scarce.[3] Assessments by PricewaterhouseCoopers, pharmaceutical corporations and the Tufts Center for the Study of Drug Development (USA) point to development costs for radical innovation (a new drug) that range between US$4.2 and US$2.6 billion, while Light and Warburton have values below US$250 million.[3] There is a variation of 1800% between these figures. This disparity is also evidenced in a research synthesis developed by the Graduate Institute, Geneva.[4]

[a] https://apps.who.int/gb/ebwha/pdf_files/WHA72/A72_R8-en.pdf

In MSF's experience, pharmaceutical and biotechnology companies often claim that the high costs of R&D – clinical trials, in particular – justify high prices for drugs and other medical tools, yet we are unable to establish the veracity of these claims because the costs of clinical trials are either not publicly available, or not disaggregated in a form that can be readily analysed and scrutinised.[5] National clinical trials regulatory framework should be amended to include mechanisms that ensure the public disclosure of the costs of clinical trials in a sufficiently disaggregated form to allow proper scrutiny.

Disaggregated information on the cost of clinical trials must be fully transparent, as a report by researchers at the New York University recommends, so that governments, public, civil society and other purchasers of medical tools can:[6]

- challenge pharmaceutical companies' justification of high prices based on high R&D costs
- determine a more accurate true cost of late-stage clinical research
- overcome information asymmetry to enable more equal and effective price regulation and negotiations
- allow the public and independent experts to compare clinical trial expenditures and identify inefficiencies
- appropriately assess the contribution of public institutions and not-for-profit research entities into clinical development.

It is important to highlight that there are examples of research organisations that disclose their clinical trials costs, such as the Drugs for Neglected Diseases initiative (DND*i*), a not-for-profit R&D organisation that develops medicines for populations affected by neglected tropical diseases. In order to foster the debate on transparency, DND*i* published its R&D costs and out-of-pocket expenses disaggregated by early discovery and clinical trial phases, differentiating between new chemical entities and existing drugs with or without new formulations, in 2014 and 2019.[7,8] DND*i* estimates it can develop and register new treatments that combine or repurpose existing drugs for €4-32 million; and a new chemical entity for €60-190 million. These figures do not include additional studies post-registration and marketing authorisation costs, nor in-kind contributions from pharmaceutical industry partners in DND*i*-led R&D projects, mostly because of lack of disclosure of such data by the pharmaceutical industry partners.

During the COVID pandemic, there have been several instances in which the lack of transparency on R&D costs has impeded access, challenged informed procurement decisions and inflated prices. For example, for tocilizumab, a monoclonal antibody therapy recommended by World Health Organization (WHO) for the treatment of COVID, pharmaceutical company Roche kept the price very high in most countries, with prices ranging from US$410 in Australia, US$646 in India to US$3,625 in the USA per dose of 600mg. However, the cost to manufacture tocilizumab is estimated to be as low as US$40 per dose of 400mg. The company has not published the actual development and clinical trial costs.[9]

Similarly, baricitinib, an oral treatment for COVID recommended by WHO as an alternative to tocilizumab, has been priced out of reach in most LMICs. Research has estimated that the cost-based production price of baricitinib can go as low as less than US$2 per 14-day treatment.[10] However, the pharmaceutical company Eli Lilly has priced this medicine at US$1,109 in the US, while generic companies in India and Bangladesh can already supply the medicine for US$6-7 for a 14-day treatment course. Some LMICs such as Argentina are paying a higher price for this medicine than some high-income countries such as the UK, Denmark and France. Eli Lilly has not published their research and development cost, including those involving clinical trials, nor provided a justification for the aforementioned high prices.

Recently, WHO has publicly expressed concern on the lack of transparency from pharmaceutical company Pfizer on nirmatrelvir/ritonavir, an oral antiviral medicine recommended by WHO to be used for people with high risk of progressing to severe COVID.[11] Pfizer has not published any information on the R&D cost of this treatment. While research has estimated the cost-based generic price of this treatment is around US$73.5 per treatment course, Pfizer is charging more than US$500 in the US market and has kept its prices in the majority of its bilateral supply agreements confidential, including reportedly pressuring UNICEF to keep the prices confidential as part of the supply deal to the ACT-A therapeutic pillar.[12]

Another example is the Oxford/AstraZeneca COVID vaccine. The company pledged to charge an at-cost price for the duration of the pandemic, and in perpetuity in a select number of LMICs. However, it has been impossible to determine the extent to which this pledge has been upheld due to the lack of transparency on the cost of development. Including transparency on R&D costs in the resolution can overcome access and affordability barriers, and enable increased efficiencies in R&D expenditure.

The above examples show that the absence of a mechanism to ensure transparency of the cost of clinical trials is a key factor contributing to the justification of high prices by industry of the end products of research and development. Disclosing clinical trial costs should be part of the legislative framework of clinical trials. Italy and France have recently put forward policies that aim to improve the transparency of R&D costs, and legislations in this regard have been proposed recently in the United States and Brazil.[13,14,15]

We suggest that the resolution include language that establishes explicit requirements for disclosure of disaggregated information of clinical trial cost, particularly when public funds, health system infrastructure, and resources have enabled the clinical trial of health interventions.

3. Diversity of populations in clinical trials

MSF supports diversity and inclusion in clinical trials as one of the guiding principles for health equity. There is a growing literature that demonstrates the importance of breaking from the traditional homogeneity in clinical trial participation to improve fairness of care, reduce outcome disparities among populations and to improve equity.[16]

DND*i*, for instance, has included within their R&D principles a commitment to gender-responsive R&D by promoting the inclusion of women, especially women of childbearing age, as early as possible, and by systematically providing disaggregated clinical trial results.

The inclusion of diverse populations in clinical trials, whenever possible and relevant, is key to a better understanding and recognition of the disparities in health outcomes originating from such differences. Transparency of, and systematic access to, disaggregated data is needed to understand the outcome of the trial on a diverse study cohort. Despite the relevance of this principle, it is important, however, to incorporate adequate flexibilities to this policy when aiming to generate expedited evidence to demonstrate efficacy and safety of technologies for tackling public health emergencies.

4. Unhindered access to comparator drugs, vaccines and diagnostics

As recently reported in Nature, DND*i* was denied access to Pfizer´s Paxlovid. The drug is used to treat COVID, and was key to the continuation of the ANTICOV clinical trial, a large study in 10 African countries that aims to find treatments for mild to moderate COVID — particularly those that will work in resource-poor settings.[17]

Additionally, generic or biosimilar pharmaceutical companies, either public or private, often face undue barriers to accessing reference products needed to carry out relevant studies, such as bioequivalence, required for regulatory approval of health technology equivalents in the field of medicines, vaccines and diagnostics.

Hence, the clinical trial resolution would greatly benefit through the adoption of recommendations and principles by WHO member states that ensure unhindered access to reference products needed for clinical trials, public health studies and/or data required for regulatory approval of technological equivalents (diagnostics, medicines and vaccines).

5. Access conditions and access and benefit-sharing principles in clinical trial design and research governance

Clinical trials increasingly involve a collaborative effort from various parties. These parties can include academic institutions, pharmaceutical and biotechnology companies, contract research organisations, product development partnerships, civil society organisations and a variety of private and public funders. Additionally, clinical trials rely heavily on existing national systems, resources and personnel to carry out such studies. These actors, together with individual clinical trial participants whose biological and genetic samples and related data are collected, collectively contribute to the end products resulting from the clinical trials. Although most national legislations assure that clinical trial participants at least have access to the health intervention trialed, if proven of health value, there are no guarantees that these health technologies will be registered where the trials occurred, made available and affordable in countries where the trials were supported, or that people in countries where the trials were held will have access to them.

To provide better accountability in ensuring accessibility and affordability of the end results from clinical trials, access and benefit-sharing principles and conditions should be incorporated centrally in the design of clinical trials and the overall R&D process. Access and benefit-sharing principles envisage the mechanism by which providers of genetic resources, biological materials, samples, genetic sequence and associated data to research should have the right to claim fair and equitable share of benefits arising from the research. The incorporation of these principles, established by the Nagoya Protocol, therefore could help ensure equity and enhance the overall governance of clinical trials, and support developing countries, communities and individuals in demanding adequate and affordable access to the end results of the trials.

These conditions of benefit sharing could also include explicit requirements on transparency, pricing, access and use of technologies and know-how, and enhancing local capacity in R&D, manufacturing and supply. Many countries have established or are in the process of strengthening national

and regional laws, policies and related mechanisms concerning access and benefit sharing, which provides an important opportunity to explore the better use of such mechanisms in the context of clinical trials.

Therefore, it is key that the clinical trial resolution reflect and incorporate access and benefit-sharing principles so as to ensure access to end products from trials by people in need.

In addition, overall access considerations, strategies and explicit conditions should be embedded as early as possible in the research design, and governed by key stakeholders across the entire R&D process. These conditions and considerations could be associated with the funding agreements of the research, the terms of the collaboration and agreements between the various stakeholders at different stages of the process, principles and provisions concerning the management of knowledge inputs and outputs, including intellectual property (IP) related to background technologies and R&D outputs, with the aim of maximising the openness of and access to knowledge. The current clinical trial resolution should take adequate consideration and reflect explicit policy requirements of strengthening access conditions in clinical trial funding and overall R&D governance.

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