ONLINE CONSULTATION

Clinical Trial Eligibility Criteria for Participants with HIV: Guidance on Improving Inclusion in Non-HIV Trials

1. Introduction and Objectives

The online consultation on the draft guidance of the *Belong* project, held on 7 October 2025 and moderated by Roger Tatoud, brought together 23 participants, including HIV and other patient community advocates, clinicians, researchers, and representatives from the pharmaceutical industry, ensuring a broad and multi-stakeholder perspective.

Nicoletta Policek, EATG Executive Director, welcomed participants and outlined the purpose of the consultation: to review the draft guidance developed aimed at encouraging European regulatory authorities, including the EMA, to adopt clinical guidelines that promote the inclusion of people living with HIV in non-HIV trials.

Since 2022, EATG has been working to address the persistent gap resulting from the frequent and often arbitrary exclusion of people living with HIV from non-HIV clinical trials. As HIV treatment has advanced, people living with HIV are living longer and increasingly experience age-related conditions, often at higher rates than the general population. Yet, exclusion from clinical research continues to limit scientific understanding, deny people living with HIV access to potentially lifesaving or life-extending medicines, and reduce the generalisability of trial findings.

The guidance remains a work in progress and is intended to complement existing frameworks, such as ICH-GCP, by promoting greater diversity, inclusion, and representativeness in clinical research globally. While applicable across all disease areas, it places particular emphasis on conditions that disproportionately affect people living with HIV.

Feedback from a preparatory survey informed the agenda, prioritising discussion of four key areas: eligibility, medical condition or disease area, clinical status, and community engagement.

2. Key Discussion Points and Recommendations

2.1 Eligibility of people living with HIV in non-HIV trials (Section 1)

- **US Context:** The US FDA guidance (CTEP guidance, focused on oncology) is seen as being "ahead" of Europe, generally advocating for the inclusion of people living with HIV who are on treatment and biologically suppressed, unless justification for exclusion is provided. However, it was noted that despite existing FDA guidance, implementation remains inconsistent, and tracking actual inclusion rates is challenging due to confidentiality surrounding HIV status See Leone *et al.*[1])
- **Europe Context:** No guidance specific on this topic. It will be important to harmonise guidance between regulatory authorities.
- **Data collection:** Participants noted the challenges of collecting reliable data, particularly due to stigma associated with HIV status, although confidentiality is guaranteed by regulation. It was also noted that the perceived low incidence of HIV among potential trial participants may lead to limited efforts to implement measures that promote the inclusion of people living with HIV.

[1] Leone AG *et al.* Inclusion of people living with HIV in Food and Drug Administration (FDA) oncology pivotal registration trials from 2020 to 2024. *Journal of Clinical Oncology* 2025; 43. DOI:10.1200/JCO.2025.43.16 suppl.1517.

- **Active Recruitment:** Participants discussed the balance between passive enrolment of people living with HIV and the need for proactive recruitment. It was suggested to strengthen the language to promote active recruitment as a key component of trial diversity and to ensure adequate representation for meaningful safety and efficacy analyses, particularly in disease areas where people living with HIV are disproportionately affected. There may be an excessive level of caution or sensitivity around including people living with HIV in non-HIV trials. The current strategies used to facilitate the enrolment of pregnant and lactating women were mentioned as a potential reference model. The World Health Organization has adopted a resolution on strengthening the clinical trials ecosystem in low- and middle-income countries, which includes the development of a framework to enhance the inclusion of children, pregnant and lactating women in research.[2]

Next Steps/Action: Work on the balance of active versus passive recruitment, address concerns about status disclosure (confidentiality), and learn from the inclusion processes developed for other populations (e.g., pregnant and lactating women).

2.2 Clinical Status: Past AIDS-Defining Illnesses (Section 6.1)

The proposed guidance suggests that people living with HIV who have no history of AIDS-Defining illnesses should generally be considered eligible, like in the CTEP guidance. If there is a history of AIDS-Defining illnesses, inclusion should consider the timing, control status, and relevance of the illness to the product tested.

- **Control of the Illness:** A distant, fully resolved illness should not preclude participation. If an AIDS-Defining illness was recent, it should ideally have been controlled for a specific period (study and product specific) before inclusion.
- **Comment:** Excluding people based on a history of AIDS-Defining illnesses can leads to over-exclusion. Other patients (e.g., those receiving cancer therapy) often have low CD4 counts, questioning why people living with HIV are held to different standards. Exclusion should be based on risk, not assumption, emphasising the need for study-specific risk assessments.

Next Steps/Action: Emphasise study-specific risk assessments. Clarify the writing related to timing of AIDS-Defining illnesses and their control.

2.3 Antiretroviral Therapy (ART) and Drug-Drug Interactions (Section 6.3)

Exclusion based purely on an ART regimen or time on ART should be avoided, as it is often subjective or unjustified. people living with HIV who are virologically suppressed should be eligible.

- **Mitigation:** The guidance should encourage trial teams to implement mitigation measures, such as switching to an alternative antiretroviral therapy (ART) regimen with fewer drug–drug interactions (for example, integrase inhibitors in oncology trials). Any modification of ART should be study specific and undertaken in consultation with HIV specialists, particularly in non-HIV clinical settings.
- **Treatment Interruption:** The possibility of ART interruption was cautioned against. Participants thought it would rarely be justified or needed, and that treatment interruption would be rare and only considered if the potential benefit of the drug dramatically outweighs the risk to the patient. Any decision to interrupt treatment must involve consultation with HIV specialists, especially in non-HIV settings.
- **Advanced Therapies:** The emerging challenges presented by advanced therapies, such as CAR T-cells, which involve complex procedures and lentiviral vectors was mentioned. The guidance may need to address potential, theoretical risks of recombination or interactions with ART in these specific, high-tech therapies, although ongoing trials suggest these are not currently insurmountable barriers.

[2] https://www.who.int/news/item/07-10-2025-who-launches-the-global-clinical-trials-forum

Next Steps/Action: Review language around treatment interruption. Emphasise study-specific risk assessments.

2.4 Comorbidities (Section 6.4)

The focus of the discussion was on managing comorbidities due to the risk of polypharmacy and drug-drug interactions. The current guidance emphasizes reviewing medical history and potentially switching treatments for comorbidities, provided the benefits outweigh the risks.

- **HIV as a Comorbidity:** A key conceptual point raised was that the guidance should avoid treating HIV as a "separate box" and instead treat it as "any other comorbidity" with its own specificity, just like any other chronic condition.

Next Steps/Action: This recommendation will be revised to reflect that HIV should be considered within the broader framework of comorbidity management, with appropriate clinical monitoring, specialist consultation, and risk mitigation strategies, rather than as an exclusion criterion.

2.5 Clinical Status: Immune Functions (Section 6.2)

The use of CD4+ T-cell count (and possibly CD4/CD8 ratio) as surrogates for immune function. The number 350 cells/mm³ was suggested as a cutoff for general eligibility (based on CTEP guidance).

- **Critique of Cutoffs:** Clinicians emphasised that reliance on a fixed CD4 threshold such as 350, even if described as flexible, often results in arbitrary and unnecessary exclusions by trialists without HIV expertise. It was recommended that the guidance reflect the CTEP position, which discourages the use of CD4 cut-offs unless scientifically justified. Further, harmonisation is important for those conducting trials across different regions.
- **Nadir/History:** Using nadir (lowest historical CD4 count) as an exclusion criterion may unfairly exclude older people living with HIV who began treatment under different guidelines when ARVs were not widely available. Furthermore, nadir is often not reliably recorded.
- **Viral Blips:** Long trials may involve participants experiencing temporary viral blips, the guidance should specify that transient viremia should not automatically result in exclusion from the trial.

Next Steps/Action: Review this section to ensure that CD4+ count and viral blips are not used as a reason for exclusion, regardless of other clinical or risk assessments.

2.6 Medical condition under investigation (Section 3)

No further comment beyond those made during the discussion in section 2.1.

2.7 Engagement of Communities of people living with HIV (Section 9 and 10)

The need for community involvement was strongly supported, emphasizing that engagement must happen early.

- **Involvement vs. Engagement:** It was suggested the guidance use the term "involve" rather than "engage," as involvement implies a stronger, two-way process where the community takes a leading role (for example in protocol design).
- **Advocacy and Awareness:** There is a need to proactively inform people living with HIV, who often assume that clinical trials are “not for us” because of their chronic condition, sometimes reinforced by the language used in trial materials (Trial recruiting “Healthy” people). This is particularly important for conditions that disproportionately affect people living with HIV, such as certain cancers and sexually transmitted infections (for example, prevention studies on doxyPEP or gonococcal vaccines).
- **Regulatory Driver:** It was stressed that the actual driver for inclusion will likely be regulatory attention, mandating the collection and reporting of inclusion data, rather than just education.

Next Steps/Action: Strengthen the language on community engagement (recommend community review of non-HIV trial protocols), and regulatory requirement for monitoring and reporting.

2.8 HIV Testing

Participants generally agreed that HIV testing should not be mandatory for all non-HIV trials. However, testing should be offered if the trial protocol poses a suspected risk specifically linked to enrolling a participant with unknown HIV status (e.g., due to potential drug-drug interactions or safety issues).

A suggestion was made to broaden this recommendation to testing for all "blood-borne viruses" (e.g., HBV, HCV, and HIV) to reduce HIV-specific stigma.

Next Steps/Action: Revise language to broaden this recommendation to testing for all "blood-borne viruses".

3. Next Steps

The notes and proposals made during the consultation will be incorporated into the guidance. The revised document is considered sufficiently robust to be presented to the EMA to prompt formal discussion and determine the regulatory steps required to advance the guidance. Further opportunities for in-person discussion may be sought at forthcoming conferences.