EATG PROMise Project

Annexe to: Recommendation Consultations Report

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PROMise

Acknowledgements

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Purpose

The report summarises discussions held with various stakeholders regarding the recommendations found in the research paper, PROMs in HIV Research and Development: Analysis of Community Needs and Engagement.

Background

EATG commissioned research to analyse the role of patient-reported outcomes (PROMs) in HIV research and development (R&D) and to explore potential contributions by community-based organisations. A narrative literature review was conducted to learn more about PROMs, including what makes a reliable and valid PROM instrument, how PROMs can act as clinical trial endpoints, and how they are being used in clinical practice and clinical research. The main take-away messages from the literature review were:

- PROMs must embody the same characteristics as other trial endpoints, including being responsive to the research question being asked.
- Changes recorded in specific domains must be attributable to the differences in the trial arms.
- PROMs must detect changes within the short timelines associated with clinical trials for HIV R&D.
- People living with HIV must be included in every aspect of PROMs, from conceptualisation to development to implementation to analysis of results. The involvement of people living with HIV in PROMs development should be seen as being analogous to the principle and practice of the greater involvement of people living with HIV (GIPA). This is to ensure that PROMs used in HIV R&D are meaningful to patients and that the checklist / research burden is minimised.

A survey was distributed to people living with HIV to find out what kinds of side effects or disturbances associated with their current treatment they would like to see eliminated. The survey also asked about people's wishes for future treatment characteristics, including the possibility for fewer molecules, fewer tablets, long-acting formulations, etc. The findings indicated that there is no consensus on either the types of disturbances that inconvenience people, nor the type of ideal treatment people would like to see in the future. This points to a reality wherein a one-size-fits all solution for future medicines discovery will not be possible.

Stakeholder evaluations with researchers, clinicians, pharmaceutical companies, and a community liaison with health technology assessment (HTA) agencies provided insights into the use of PROMs in HIV R&D from different perspectives. Researchers indicated that PROMs need to be designed to measure what they are intended to measure if they will be used as primary endpoints. Current PROMs are used as secondary and exploratory endpoints and are constrained by attribution and timeline challenges. Clinicians underscored the need for diverse treatment options because patients have diverse needs. Pharmaceutical companies indicated that it is difficult to design trials that use PROMs because guidance from regulators is currently insufficient. The HTA agency community liaison pointed to the fact that generic PROMs allow for comparisons across disease states and that, for reimbursement, PROMs need to be linked with clinical outcomes and not just patient preferences.

As a result, the author of the research paper and the EATG PROMise Task Force developed a set of recommendations from a community perspective aimed at stakeholders, including community-based organisations, to further develop PROMs in HIV R&D so that they better meet the needs of people living with HIV. It was decided to take these recommendations to various stakeholders to get their input and endorsement.

Methods

The recommendations were presented during a workshop at the 2021 EACS meeting in London with participants both onsite and online. The recommendations were updated based on feedback from this session and presented at the following focus groups in subsequent virtual meetings: Researchers and Clinicians; Pharmaceutical Companies; and the EATG PROMise Task Group.

Results

ECAS Workshop

Total participants: **136**

People living with HIV/Community: **44%**

Clinician: **13%**

Researcher: **13%**

Pharmaceutical company employee or consultant: **26%**

Regulator/HTA employee or consultant: **4%**

Kevin Moody presented a summary of the project and its results after which participants provided feedback via a poll that was accessible in the room and virtually. The questions posed summarised the recommendations in the research paper and responses were provided by between 15 and 23 members of the onsite and online participants. From the polls, all the recommendations were validated, except one that dealt with community-based organisations. The summary recommendation presented at the workshop stated, "What is the most important area that community organisations should take the lead in investigating?". The option, "Types of disturbances (side effects) that people living with HIV would prioritise to be resolved with new types of treatment" garnered no support.

During the panel discussion portion of the workshop, panellists Caroline Sabin (researcher), Felipe Rogatto (pharmaceutical companies) and Ian Hodgson (community) responded to questions from the facilitator and from onsite and online participants. This discussion further confirmed many of the recommendations but notably introduced a new recommendation. The overwhelming consensus from the participants and presenters was that a dialogue among all stakeholders was needed to define next steps in terms of moving forward with the issue of PROMs in HIV R&D. Specifically, participants felt that there was a need to define and reach consensus on the characteristics of PROMs that should be used in R&D and to engage with regulators so that sufficient guidance can be provided.

The workshop led to the revision of the recommendations, with the removal of the rejected community-based recommendation plus the addition of an overarching recommendation to engage in multi-stakeholder dialogue.

Research & Clinician Focus Group

Participants:
Diana Barger, University of Bordeaux
Giovanni Guaraldi, University of Modena and Reggio Emilia
Caroline Sabin, University College London
Guido van den Berk, OLVG Hospital, Amsterdam

Summary of points made by participants

- Need for a standard set of PROMs in HIV R&D to ensure consistent reporting in trials and to avoid bespoke PROMs that test for a specific desirable characteristic in a new product.
- There is currently no consensus on the use of PROMs in routine HIV clinical care.

- Important to start the dialogue with key stakeholders, including companies, researchers, and community, to be able to present something concrete to regulators so that they can provide guidance.
- A Delphi process could be useful to explore desirable characteristics of PROMs and to build consensus. The resulting publication would be a good tool to engage regulators if they choose not to participate in the Delphi process from the beginning.
- It is essential that the wish list of PROMs does not lead to many instruments and items that are required for R&D trials to ensure that PROMs are meaningful to people living with HIV and to minimise research burden. Pharmaceutical companies must be able to differentiate new products, but not increase the burden of trial participants.
- A consensus-building process would help to understand the potential impact that treatment has on people and narrowing down the domains in the PROMs to get to a shorter number of items. This would be a starting point to agree on characteristics and domains that would be included in PROMs.
- There are a lot of tools out there already and developing a new PROMs takes years. Therefore, it is important to anticipate the innovation pipeline and identify PROMs that that will remain relevant or develop new ones that will be relevant in the future.
- Most PROMs in HIV look at physical, psychosocial, and emotional domains. It will become important in the future to also add social domains that are related to people's preference for injectables or other long-acting products. Social domains should be related to physical and psychosocial ones by understanding the biology of people's stress response. It is all connected.
- Ecological momentary assessment is becoming an important consideration in the administration of PROMs. Technology allows for real-time gathering of PROMs through smart speaker devices in the home (e.g. Amazon Alexa, Google Nest) that can be programmed to ask PROMs questions and through wearables, which record vitals, such as pulse, blood oxygenation, etc.
- From a policy perspective, the 4th 90 (the target to ensure 90% of people living with HIV have a good quality of life) should be officially added to the continuum of care.
- Translating a PROM into a tool that relates to medicine pricing should be investigated to address issues related to HTA agencies and reimbursement. Involving health economists in this work might be helpful to make this link.
- EATG should organise a formal half-day meeting, including all stakeholders that have participated so far but also health economists.

Pharmaceutical Companies Focus Group

Participants:
Jean Marie Arduino, Merck Sharp & Dohme
Erik Chan, Janssen Pharmaceuticals
Christina Donatti, ViiV Healthcare
Bryn Jones, ViiV Healthcare
Hal Martin, Gilead Sciences
Felipe Rogatto, Gilead Sciences
Sarah Smith, Janssen Pharmaceuticals

Summary of points made by participants

- Many PROMs currently being used in HIV R&D are old instruments that are no longer relevant.
- Current PROMs have too many items and take too long to complete.
- It would be more desirable for academics or regulators to develop new instruments because anything developed in-house by pharmaceutical companies could be seen as biased.
- One option could be to work with a think tank like the King's Fund or Wilton Park to raise the profile of a multi-stakeholder consultation.
- It is too soon to start to build consensus on accepting one PROMs or a set of PROMs as the standard.
- Regulators will need something tangible, like a report or a discussion paper, if they are going to respond.
- Wellbeing and quality of life are hard to measure and difficult to attribute to specific treatment options.
- There was a difference of opinion regarding the differences between PROMs for clinical use and those for R&D:

> On the one hand, PROMs used to measure quality of life should be the same for both. The question is whether a standard set of PROMs could be agreed upon. It would also be important to come to an agreement as to which quality of life domains (physical, psychosocial, and emotional) should be measured. If instruments cannot be responsive to trial timelines and attributable to trial arms, then they cannot be used for product differentiation. However, they can be important in trials as part of standard routine clinical care.

> On the other hand, PROMs used to differentiate products based on specific product characteristics need to be different than PROMs used in clinical trials. There was a discussion about the "self-serving" nature of using these types of PROMs because of their potential bias. For instance, people entering a trial for injectables are already indicating their willingness to be injected on a regular basis. However, if PROMs are going to be used as primary or secondary endpoints to prove product superiority, they will need to be responsive to a particular product characteristic.

- Engaging regulators can only happen with collaborative activities therefore, it is now too early to expect them to engage before that has been formed. Once a product has been developed and published, we could challenge the current situation and get regulators involved.
- The FDA has conducted patient-focussed drug development meetings. The last one for HIV was in 2013. It might be possible to convince them to conduct a process around PROMs.

EATG PROMise Task Group

Participants (all EATG members):
Maryan Said, Norway
Raminta Stuikyte, Lithuania
Alain Volny-Anne, France
Brian West, Scotland

Summary of points made by participants

- EATG should talk about PROMs for HIV R&D in the greater context of PROMs for clinical care and also advances in service delivery. EATG's programmes – Partners in Science, Quality of Life, and Combination Prevention – allow for this bigger strategic view.
- Quality of life is bigger than measuring instruments like PROMs. It is important to take a broader scope and look at new service delivery modes such as video consultations, direct video observed therapy, and long-acting formulations. This would also be related to PrEP and prevention.
- The fact that regulators have not participated in the consultations, means guidelines cannot be formed. EATG should reach out to EMA again, via internal connections.

- The approach to regulators needs to be two-pronged, through science and advocacy. EATG, in consultation with the other stakeholders, needs to develop and agree on a product or a process that is evidence-based and credible and then use that information for advocacy purposes. Parallel to this, it is critical to better understand their process so that we know when we can best engage in dialogue and have influence.
- Looking outside of the EU, we could also engage WHO, which is also a regulator. It could also be helpful to engage with partners, especially in EECA, as the region is now in the middle of a process to harmonise regulatory processes.
- EATG has a history of conducting successful workshops with stakeholders. The EATG-led Sitges workshop on Hepatitis C R&D included representation from EMA. EATG could follow this process.
- EATG should engage with European patient/community organisations, including those who have strong connections with the EMA.

Discussion

Clinical versus R&D PROMs

1 Conflation of PROMs for clinical use versus R&D took place in all consultations. PROMs can be used for:

a. Health-related quality of life (HRQoL) during a clinical trial. Given the short timelines, HRQoL in the context of a clinical trial should be regarded as a necessary component of good routine clinical care and not necessarily an outcome of a clinical trial. As explained in the HIV R&D research paper, most HRQoL PROMs for HIV measure physical, psychosocial and emotional issues that do not change in short timelines. However, if a new product or approach is developed that can make a difference in an HRQoL domain, then the PROM could be used as both a clinical tool and a clinical research endpoint.

b. Identifying patient preferences, treatment satisfaction. These PROMs might be useful, and this should be investigated. If not, then they should not be included.

c. Differentiating new products from existing ones with specialised PROMs especially intended for a particular product. Examples include PROMs for pain or injection acceptability for injectables and PROMs for sleep disturbances. If a product is developed to address these specific domains, PROMs can be used in clinical trials to differentiate those products from existing ones based.

2 By not addressing these uses separately, it makes discussions and strategic planning for advocacy and guidance confusing.

3 The current focus should remain on R&D and the discussions should explore the reasons for using PROMs and the characteristics of good PROMs for each specific use.

4 To finish this stage of the work in a meaningful way, EATG should not include other issues important to the community that are not directly related to HIV R&D, including digitisation of service delivery, general quality of life, etc.

Stakeholder Workshop

1 **Consensus from all consultations that a stakeholder workshop is an important next step.**

2 **There are differing ideas of who should participate and what the agenda should look like.**

a. **Participants:** Some think that outside facilitators, such as think tanks, should be involved. Others have suggested health economists to make the link between PROMs and financial aspects. There was no consensus of how and when to involve regulators in a stakeholder meeting, although the community has been successful in engaging them in the past.

b. **Agenda:** The researchers have suggested that the meeting could be the start of a Delphi process. Others suggest that the meeting should provide an opportunity to "hash things out" between relevant stakeholders. The Delphi process is not well understood by most stakeholders.

3 Jeffrey Lazarus held a multi-stakeholder meeting in collaboration with Wilton Park. The agenda and report can be found here. This meeting was designed to kick off another consensus-building process around digitisation of care, which will likely be in the form of a Delphi process, similar to his work on quality of life from 2021. This approach can be explained and discussed at the multistakeholder workshop, to see if it is an option for the next steps to finalising the work.

Regulators

1 There was no consensus on how to engage regulators, except that there needs to be something substantial for them to react to. However, there was no consensus on what this product or process should look like. In the past, EATG successfully engaged regulators in specific forums with specific conditions, for example in a workshop setting where the regulator could speak off the record. However, even in this case, EATG did not manage to get regulators engaged in the debate despite a few efforts.

Conclusions

1 **Hold a stakeholder workshop before Summer 2022. The PROMise Task Group has suggested June 2022.**

2 **Meeting objective:**

a. Develop a consensus-building process for exploring and defining:

- **i.** the various uses of PROMs in HIV R&D (see definitions under Discussion-Clinical versus R&D PROMs-point #1)
- **ii.** the characteristics that PROMs should have for each specific use, including domains, length, research burden, involvement of community, etc.

3 **Participants:**

a. All current stakeholder participants or representatives, including the individual who participated from the Health Technology and Assessment International (HTAi) Patient and Citizen Involvement in the HTA Interest Group

b. Consider expanding to include other disciplines, for example health economists, as well as other patient groups.

c. Consider reaching out to a think tank to get them involved.

d. Invite regulators but manage their expectations beforehand by sharing the meeting objective. It is important that they realise they are part of a formative process and will not be asked to endorse anything.

4 Agenda:

a. Define the various uses of PROMs in HIV R&D trials.

- **i.** HRQoL
- **ii.** Preference, satisfaction
- **iii.** Product-specific to differentiate new products from existing ones

b. Begin defining the desirable characteristics of these different types of PROMs, in smaller groups within the big room or in breakout rooms. Define the various uses of PROMs in HIV R&D trials.

c. Discuss various possible methodologies, including a Delphi process, for working toward consensus of the categorisation of PROMs use and their characteristics and agree on which methodology should be used moving forward.

4 Outputs:

a. A detailed workplan describing a process over the next several months (following the multistakeholder workshop) to collect evidence from stakeholders regarding their position on the various uses of PROMs in HIV R&D and the characteristics of these PROMs by use category. This will require further fundraising.

b. By mid-October, publish a consensus statement, either in a reputable journal or via a concerted communications strategy.


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