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Where to from here: Advancing patient and public involvement in health technology assessment (HTA) following the COVID-19 pandemic

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Where to from here: Advancing patient and public involvement in health technology assessment (HTA) following the COVID-19 pandemic

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Editorial: Where to from here: Advancing patient and public involvement in health technology assessment (HTA) following the COVID-19 pandemic

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KEYWORDS

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Editorial on the Research Topic
Where to from here: Advancing patient and public involvement in health technology assessment (HTA) following the COVID-19 pandemic

Where we have been, possibilities ahead

The COVID-19 pandemic brought with it challenges for science, vaccine development, therapeutics, and evidence-informed health care. Ethical and moral issues were at the forefront, particularly around vulnerable populations, equity, and involvement of patients and patient advocates in decision making individually and at policy level. Patient advocates and patient partners often found themselves shut out from decision-making processes in a situation where systems were overwhelmed, but at a time when advocacy and partnership were arguably most needed. Shortages of personal protective equipment (PPE) and limited knowledge of the virus meant that patients often died in hospitals without their families and significant others around them (1).

Patient advocates, patient partners and leaders however continued to be active throughout the pandemic. An example is where Australian consumer representatives, including from rural and regional areas and diverse cultural backgrounds, organised themselves to work with communities to identify inadequate or inappropriate aspects of patient care during the pandemic (2). They filled an important information and communication void and were also able to mobilize support from communities and politicians to address specific healthcare issues in local areas. In Québec, a "community of practices on patient experience and patient engagement" created a "white book" to share innovations focussing on how to maintain patient partnership at all levels of the healthcare system even in a pandemic (3).

We proposed the present Research Topic at the beginning of the COVID-19 pandemic, without foresight of the impacts it would have on communications in health care at all levels,

including required regulatory and health technology and value assessment processes. And so the question "where to from here" with patient advocacy and community input continues to be relevant. Methodologies and opportunities are outlined in the included articles from around the globe.

Maintaining the link with patients

Articles show that groups in Canada were able to recognise the strengths of their patient partners and patient experts to work together in designing communication pathways and technology-based services (Barony Sanchez et al.) as well as address policy issues and evaluation of promising interventions (Olivier et al.). Communication with diverse communities has been essential to transfer information to the public over the course of the pandemic. Barony Sanchez et al. describe how researchers in the province of Québec engaged co-creatively with patients and public partners with different backgrounds and literacy levels to develop and promote access to online health care through a "shared virtual space". The leap to digital technology was essential because of restrictions in people's movements, particularly for those most at risk, the need for rapid access to care, and for better resource utilization. For a digital technology to be useful and effective, it has to be able to attract and actively immerse the user in its content.

Decision-making process issues in HTA agencies

In Québec, the responsibility for managing the pandemic lay primarily with policy-making bodies, healthcare facilities, health ministries, regulatory bodies and agencies. Olivier et al. describe how the Institut national d'excellence en santé et en services sociaux (INESSS) played a key role in informing government on the evaluation of pandemic-related interventions. Ethicists, clinicians, patients and citizens with patient-partner expertise helped identify uncertainties and ethical considerations. Patient and citizen perspectives contributed to shifts in thinking for benefit-risk assessment of promising interventions, being strongly in favour of individual responsibility, shared decision between clinicians and patients, and the expression of free informed consent. Greater transparency in communications, not subject to media or political pressure, could reduce the risk of medical misinformation. Cellier expands on the principles behind patient involvement throughout health technology assessment (HTA) and value assessment of medical products within a healthcare system. These are necessary for fair and reasonable decisions. The Taiwan Division of HTA, Center for Drug Evaluation continued activities to improve patient involvement in their HTA processes, to enable effective and meaningful involvement with patients, carers and communities through online interactions, virtual meetings and cooperation with patients' organizations (Chen et al.).

Digital technology and accessibility

The patient and public involvement team at the UK National Institute for Health and Care Excellence (NICE) were quick to adapt to online meetings and virtual engagement (Rasburn et al.). They identified benefits, including enhanced accessibility without the need to travel, and so removal of barriers preventing participation by patients and carers. Participants could now control conference tool settings (e.g., sound, camera) and feel comfortable in their own environment. Furthermore, more people were able to attend and observe meetings. Drawbacks include restricted opportunities for networking, brainstorming, and inability to read body language and non-verbal communication.

Communication of relevance and value of patient input

Early in the pandemic, NICE demonstrated to committee members the value of patient advocate members through a role-play exercise (Rasburn et al.). Brazilian women with breast cancer highlight the importance of understanding what clinical trial outcomes mean to patients (Silva et al.). Wale et al. describe from a patient advocate perspective how patient experiences can inform the value of medical products for HTAs. Where much effort has gone into increasing our understanding and use of patient experience data, including patient preference studies, patient reported outcome measures, and patient-focused registries. Patient experiences and knowledge are important to determine the relevance of evidence to clinical practice, democratize and build on the legitimacy of HTAs.

Changes in research methods

Regulatory and HTA bodies concentrate on evidence from randomised controlled trials to determine overall benefits and risks for individuals. Courcelles et al. propose computerised modelling to address uncertainties in the evidence and predict effectiveness in individual patient groups in clinical care—considering epidemiology, a range of "standard of care" options, and longer-term effects.

The COVID burden

Stresses caused by the pandemic on social and healthcare services continue to be evident, and with large numbers experiencing long-term consequences of COVID-19 infection (4). Many of the world's populations are not supported by strong health systems. In the African region, Sehmi and Wale utilised World Health Organization National Medicines Policies to highlight some of the issues in access to medical products and providing health care. In a second paper, they and other authors

highlight how local manufacturing and strong regulatory lifecycle processes, with civil society involvement, could help (Wale et al.). Human rights to health care and participation in decision making at a local level are important.

The Research Topic effectively demonstrates the importance of patient advocates, patient partners and civil society during a pandemic, with mutual value to all.

Author contributions

JW and M-PP contributed equally to the writing of this Editorial. All authors contributed to the article and approved the submitted version.

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OPINION
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The Place and Importance of Patients in Deliberative Processes

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Keywords: patient partnership, patient and public involvement, ethics, deliberative process, HTA, decision making

INTRODUCTION

"Perhaps the most notable wake-up call of all is inequity, as the worm in the heart of the world" (1). In the last year and a half, healthcare systems worldwide have been confronted to countless challenges and to the realization that their ways of making decisions are not always in line with the population's context, needs and priorities. As has been established in the past, patients being the main concerned stakeholders in the delivery of their care, not only is it their right to be included in deliberative processes that will impact them (2), their implication and the insight they provide are the key to ethical decision making, which is the only sustainable solution to inequities in healthcare. However, patient involvement is not sufficient to ensure accurate and long-lasting representativity of the population's needs and priorities. As was identified in 2020 (3), the "Need to design better approaches to involve stakeholders in HTA" is a major challenge of health technology assessment (HTA). INAHTA recently released a position statement on the subject, and recognized patient involvement as an "important and valuable element in the conduct of HTA," providing a list of important considerations for meaningful patient involvement (4). In addition, a collective reflection on legitimacy, values and patient involvement in HTA, including in deliberation for clinical practice guidelines (CPG), was proposed to tackle ethical challenges and develop deliberative processes focused on patients and population needs (5). If a decision is to be fair and reasonable, as defined by the ethical framework accountability for reasonableness (A4R) (6), a consistent and long-term partnership with patients, implying collaboration, communication and ensuring patients are listened to, must be applied throughout every step of the deliberative process.

Any partnership starts with a respectful relationship and implies equal collaboration. If decisions in healthcare are made based on anything other than an accurate representation of the contexts, priorities and needs of the impacted population, when translated into policy, there will be oversights of potentially essential principles, and therefore failures in providing the best care for the largest population possible. Oversights of certain specifics which make care acceptable and efficient for all are understandably made when patients are not involved, or if their involvement is limited, because no matter how good the intentions, experts in deliberative processes lack outside view of the results of decisions that are made, and of the receiving end of their translation into policy and care.

DELIBERATIVE PROCESSES

Because of the complexity of deliberation processes, patients are rarely involved beyond a consultation role, which is indeed essential, but is limited in its impact and cannot ensure sufficient representativity of the needs of the population to determine the best possible provision of care. The experiential knowledge patients can provide in the form of data can shape deliberative processes and provide a strong base for understanding their context and for prioritization of their needs. However, the accuracy and value of this data is determined by its representativity of the actual population, which requires an adequate diversification process to ensure all voices are heard. Every sub-group, determined by diversification criteria applied to a general population, must be able to

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provide their opinions and insights in an environment conducive to debate and discussion on what they need and what the deliberative process should prioritize in further steps.

An ethical framework designed to assess how an intervention contributes to the foundational objective of healthcare systems through several dimensions (7) provides a single structured method to be used for every step of a deliberative process. Such structure is essential to ensure continuity and coherence, to provide a tool for collection, analysis, and synthesis of data, as well as a basis for discussion through deliberation. The analysis of data is the core of deliberative processes and must therefore be able to identify the essential aspects and priorities to be considered in the making of decisions. Data collected throughout the initial steps of deliberative processes must then be synthesized in order to see emerge the essential points and considerations to be taken into account for accurate decision making, and to ensure the result is applicable in the context of the population and in line with its current needs.

To allow key aspects to emerge, they must be organized in a way that can reveal where gaps are in the current context of the population, and where inconsistencies or issues in the delivery of care must be addressed. The essential points and considerations identified through the analysis can therefore be prioritized to facilitate the decision making process. The insight and the opinions of patients throughout this process are essential to ensure that the prioritization of these key arguments is representative of what their needs and priorities are. However, if patients are consulted to provide data that will only be used to fill potential gaps in the research, or as a way to justify decisions that, in the end, aren't in line with what they ask for or what they need, there's no point. Structuring the data in a framework prevents this from happening, and will allow for conducive and consistent partnership with patients throughout each step of the deliberative process if the tools for the collection of data, for its analysis and for the synthesis, are constructed following the same structure and are organized in linear steps, in order to follow a logical train of thought which can ensure nothing gets lost in translation.

A multi-dimensional method following this principle provides a way to reflect on every aspect of healthcare provision, such as the current socio-political context, the populational contexts, needs and priorities, clinical benefits, constraints and acceptability, as well as organizational and economic requirements. Experiential data and insights provided by patients impact on every one of these dimensions and help avoid any oversight of seemingly small or insignificant detail that could impact their care or its provision, as well as ensure no erroneous assumptions will be made regarding the needs of the target population. These five dimensions, Socio-political, Populational, Clinical, Organizational and Economic, put together, are the pillars upon which rest fair and reasonable decisions (7) when they are used for careful consideration of every aspect of care as identified by the patients, of their potential or reported impacts, and of all necessary requirements for sustainable and acceptable provision of care within the healthcare system. The acceptability of care is central to making informed decisions regarding its provision since it's defined by individual experience of care and its impacts. However, experts in deliberative processes alone cannot ensure that patients' needs and priorities are at the center of the entire process, especially when HTA processes have had a tendency to focus on quantitative scientific literature to sustain their conclusions, as has been the traditional way for most of HTA natural history (8).

A method which allows all types of data to be analyzed in the same way creates an ensemble view of the subject and of all its implications. Looking at every aspect of provision of care is paramount to make decisions which will be in line with the population and their needs. This is why patients must be involved in the process of data analysis; to provide insight for every one of these aspects, to validate the prioritization of key points emerging from the data, and to ensure the needs of the population are kept at the top of the list of prioritized aspects to be considered and discussed in final decision making processes.

The deliberative process' final step is the deliberation itself, where aspects which have been qualified as essential through analysis and synthesis of the data are discussed, and conclusions are made in order to make informed decisions. When patients are involved in the deliberation discussions, as a way to validate the interpretations of conclusions made from prioritization of key aspects through the analysis and synthesis, they can maintain the population's needs at the center of the discussions, and as resulting basis for decision making, which can avoid making decisions that could have been made based on biased views of the quality or importance of different types of data. Such decisions, which are "evidence-informed" (9), but not patient centered can result in translation into policy and care that would not answer all the needs, communicated by the patients, of the target population, which is neither fair nor reasonable. An ethical decision in healthcare can only be made through careful consideration of the needs and priorities of the population it impacts.

The key issue is that patients are seldom solicited to participate in reflection on every dimension of a subject (sociocultural, populational, clinical, organizational, economic) during a deliberation, and thus are not empowered to contribute to the balancing act that leads to fair and reasonable decisions. A recent example demonstrated that it is possible to do so by cultivating a relationship with key patients, representative the entire population, throughout every step of the deliberative process, starting from engaging into meaningful discussion during the consultation and data collection process, up to the deliberation, hence giving them the opportunity to stand their grounds in the presence of healthcare professionals and/or experts included around the deliberative table. With attentive and respectful listening to patients' experiential knowledge and viewpoints, assumptions regarding what is best or preferred by patients made without their direct perspective no longer have their place in the discussion, and the legitimacy, fairness and usefulness of the decisions are enhanced (10).

DISCUSSION

It can often be believed that decisions in healthcare are unfortunately not always solely based on patient best interest and

welfare (6), which is a grave deviation from the very purpose of our healthcare systems, and needs to be remedied. Every decision made in healthcare that translates into policy and care impacts patients, and they must be present at every step of the deliberative processes leading up to decision making, since their presence can lead to avoiding countless opportunities for oversights, assumptions or misinterpretations which can have dramatic repercussions if not caught. The objective of HTA has always been to try and determine the best ways to provide care to patients, which has often been articulated as the Triple Aim: Care; improving the individual experience of care, Health; improving the health of populations and Cost; reducing the cost of care for populations (11). The best way to satisfy these conditions is quite simple when considering its basic principle: providing the best care, for the most people, spending the least money. Improving the individual experience of care for patients is something only they can determine how to do, and which can be implemented through considering their perspectives and advice on how to best satisfy the different needs of the population when developing the specific aspects of provision of care. Improving the health of the population requires accessible and acceptable care for all concerned patients, which in turn depends on developing the best possible individual experience of care for the entire population. Finally, reducing cost of care implies sustainability on the long-term of the most acceptable and efficient version of care, which is determined by the optimal individual experience of care. The careful consideration of insights and experiential knowledge provided by patients on their own care, based on their needs and priorities, throughout deliberative processes and final decision making regarding development and provision of care is a step toward ensuring these aims being met. HTA is a process which, by definition, can always be improved (12).

Although it is methodology experts who develop, apply and improve methods used in these processes, the patients are the ones who live with the decisions that are made, and the ones best suited to determine whether they will improve healthcare (13). Developing a solid and, most importantly, equal partnership of collaboration and respect with patients throughout these processes is key to making truly representative and therefore ethical decisions for everyone.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Innovative Patient Involvement During Covid-19: Keeping Patients at the Heart of HTA

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The COVID-19 pandemic and lockdown measures in the United Kingdom resulted in significant challenges and created opportunities for innovation to keep patients at the heart of HTA. The introduction of the Coronavirus Act 2020 and the associated public health guidance meant that NICE's conventional HTA methods were no longer feasible. NICE introduced rapid, innovative updates to patient and public involvement (PPI), decision-making meetings, and consultations to harness the expertise of patients and the public to ensure guidance addressed the expected concerns and identified barriers which could impact access. This article describes the PPI support for NICE's rapid shift to virtual meetings and virtual engagement. We utilize the authors' experience and patient and public contributor feedback to understand the experience of participating in a virtual setting and identify four themes: accessibility; inclusivity; transparency; and intrapersonal relationships and committee dynamics. The article also considers how patient representatives participated in, and facilitated, the development of guidance for a hypothetical technology to keep patients and the public at the heart of expedited and novel HTA processes to identify and understand the expected patient concerns and potential barriers for when a technology would be introduced.

Keywords: PPI, health technology assessment, patient value, capacity building, new technologies

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INTRODUCTION

> *"In the early days, watching Covid−19 move through the world was like seeing the flood coming. We needed to build an ark around us and get underway at the same time as the waters were rising and the environment changing in unexpected ways while also exposing traditional fault lines of health and socio-economic inequalities."* NICE patient and public committee member

The National Institute for Health and Care Excellence (NICE) is a world leader in patient and public involvement (PPI) in health technology assessments (HTAs). NICE has pioneered the innovation, iterative development, and evaluation of best practice in all its methods and processes so that the values and standards of meaningful PPI (1) are embedded as a core principle (2).

NICE's PPI framework solicits and incorporates the expertise, experiences and perspectives of lay people, patients and carers, and patient organizations at multiple stages in the HTA process; centers their needs; and acknowledges the outcomes they value most (3).

The exigencies of the COVID-19 pandemic motivated NICE to review and systematically revise its HTA processes to ensure continuity of its mission to support the health care system and provide timely access to effective technologies for patients and the public.

The introduction of the Coronavirus Act 2020 (4) and the associated public health guidance (5) meant that NICE's conventional HTA methods were no longer feasible. NICE introduced rapid, innovative updates to PPI, decision-making meetings, and consultations to harness the expertise of patients and the public to ensure guidance addressed the expected concerns and identified barriers which could impact access. NICE had to continuously evaluate and analyze the impact on PPI and patient contributors and introduced measures to mitigate risk of exclusion and avoid tokenistic involvement. Due to the rapid nature of the updates some of these measures were reactive and implemented at various stages as the organization adapted to the new ways of working.

NICE recognized the potential of new forms of collaboration to disrupt previously identified barriers to PPI such as the resource-intensive need to attend in-person meetings (6). The COVID−19 syndemic (7) also challenged NICE to create a framework to develop guidance for technologies that did not yet exist, and maintain its commitment to PPI, leveraging the expertise of patients and the public to anticipate and address barriers which could impact patient access to such technologies.

The authors of this article are NICE public involvement staff, HTA committee lay members, patient experts and representatives from patient organizations. We describe and reflect on the successes and challenges for keeping patients and the public at the heart of expedited and novel HTA processes by reviewing two innovative approaches; NICE's rapid shift to virtual meetings and virtual engagement, and how we participated in, and facilitated, the development of guidance for a hypothetical technology.

INNOVATION ONE: INTRODUCING VIRTUAL MEETINGS AND ENGAGEMENT

The first virtual committee meeting NICE held took place on the 24 March 2020 (8). The format of virtual meetings replicated physical meetings; the agenda followed the same structure, the duration of meetings remained the same, and NICE's patient and public involvement principles (9) remained consistent.

Adapting quickly to introduce and support virtual committee meetings and virtual engagement for the first time after more than two decades of physical meetings meant NICE had to learn in real-time what the technology and training requirements were, and the necessary support committee members and stakeholders required to meaningfully engage in this innovative approach.

NICE needed to continuously review individual needs, from ensuring people had the necessary devices and connectivity to enable them to engage, and competence in the use of the virtual engagement software. NICE also needed to understand the differences between virtual meetings and physical meetings that might impact meaningful involvement.

NICE now has 18 months of data capturing the experiences of those involved in virtual committee meetings and virtual engagement to inform the evolution of our processes. The data was generated through exit surveys completed by patient and public contributors to understand their experience of participating in a virtual setting and then thematically analyzed. The data, and the perspective of the authors, has identified notable differences that can be themed into four areas:

(1) accessibility
(2) inclusivity
(3) transparency
(4) intrapersonal relationships and committee dynamics.

Accessibility

From a patient and public perspective, virtual meetings enable greater accessibility and remove barriers that may have prevented or restricted involvement. This is most notable in the removal of the need to travel to physical meetings.

It is recognized that HTAs require evidence from patients with lived experience to reflect on what it is like to live with a condition in real life. Not only does this provide a wider perspective and add to the evidence, but it can also help clarify the circumstances in which different types of evidence have strengths or limitations (10).

Often those with the required lived experience are unable to attend physical meetings, particularly those who have health-related challenges. In addition to attending a meeting, participants would also be required to travel to a physical meeting space; a barrier that restricts the ability to participate in a meeting. Virtual meetings have removed the need to travel, making the opportunity to attend and participate in meetings accessible as it can reduce fatigue and recovery time, which is particularly important to people living with disabilities, long term conditions or side-effects of some treatments.

This has wide-ranging benefits, not just to those with health-related challenges. The removal of travel also removes the geographical barrier that may have prevented participation. This is especially beneficial to those who may live long distances away from the physical meeting space, or those in rural communities and those with limited transport links.

The virtual setting provides an improved opportunity for people to participate, no matter where they are located. This can increase the patient and public population HTA bodies are able to reach, therefore increasing the opportunity to gather a wider range of views and experiences. This increased reach can identify additional needs and outcomes valued most to better reflect patients and the public.

The removal of travel also introduces time-saving benefits. Not only has this been noted to reduce the stress created by the need to travel and ensure arrival on time, but it also enables participants to better manage other commitments and reduces the need to organize additional arrangements. An example of this is those with caring responsibilities or those who need to take leave from work. Virtual committees eliminate the time commitments associated with travel, resulting in a reduction of the total time it takes to participate in a HTA. Participants have

reported the removal of travel has enabled them to allocate that time for increased preparation, both by reading the committee materials and getting mentally prepared.

From an administrative perspective, virtual meetings reduce some of the financial costs required for getting people to a physical space, such as the travel bookings, accommodation, and subsistence allowance. Whilst these cost-saving benefits may impact HTA bodies to a higher degree, the removal of financial burdens for participants has a notable benefit to improving accessibility.

Whilst NICE already had a policy to provide travel and accommodation costs upfront (11), additional costs that required up-front payment, such as sustenance allowances, could be a financial barrier to those from lower socio-economic groups. Removing the potential financial burden can aid in removing this barrier to involvement and support equal opportunity.

Virtual meetings do present additional risks of exclusion. One risk is excluding those who have low digital literacy or do not have the financial resources to participate virtually, such as not owning a computer and experiencing data poverty. Another risk is excluding those who do not have a quiet or private space to participate in virtual meetings.

Whilst NICE uses a video teleconference platform that is free for external audiences, participants still require the hardware to enable them to participate and the knowledge to use the software. To mitigate this potential barrier, NICE introduced reasonable adjustments to offer additional support to ensure participants had the resources to be able to attend. This included providing reasonable expenses to ensure there was not an inequality to participation due to communication technology poverty and relatively poor digital infrastructure, such as not having access to a computer or a reliable internet connection. NICE also introduced technical training before meetings to ensure participants can use the software and provides live technical support.

Another risk was excluding parents or carers who might otherwise have had complex care arrangements. As well as the difficulty of engaging parents who needed to home-school, some participants still needed to book a carer to have privacy and be able to have full attention at meetings; something which was not always possible with lockdown restrictions.

Some participants have also highlighted that reading documents on a screen can be difficult, especially for those who are color blind and need documents printed in an appropriate color and contrast. Due to the social distancing measures that meant staff worked remotely, NICE was unable to access printing facilities. Instead, NICE introduced reimbursement in the form of printing allowance to ensure participants who needed this accommodation could claim this back.

Inclusivity

Virtual meetings are felt to be more accessible and inclusive. This allows for greater representation of input from all, which supports our values and behaviors of inclusivity, equality and diversity that guide our work, and supports our charter that values the input from patients, carers, and the public (12).

Participants have reported a greater sense of comfort when participating in meetings, resulting in a reduced feeling that involvement is daunting. People can participate from home, so they are able to have greater control over the environment, such as using their own furniture, control the temperature, move around freely, and take additional rest breaks.

There have been notable changes in the facilitation of committee meetings. In physical meetings, people with hearing difficulties relied on adjustments, such as seating arrangements and assistive technologies such as hearing loops. In virtual settings, participants have full control in adjusting the settings to enable them to better participate. An example of this is being able to adjust the volume on their computer to improve audibility and hear everyone clearly. The front-facing camera, and ability to see the person speaking on full screen, also enables people who lip-read the ability to better view those who are speaking, as opposed to sitting around a table with various obstructions blocking their line of vision. To achieve the maximum benefit in this area, all participants are required to have appropriate lighting and be fully in the center of the frame when speaking.

There are also benefits in virtual meeting functions, such as the "raised hand" function. This notifies the Chair that participants would like to speak, and places them in a queue in order of who raised their virtual hand first. This ensures Chairs can see when someone wants to speak, which reduces participants needing to try and notify the Chair. It also disrupts the hierarchy of speakers and disproportionately dominant contributors by clearly indicating who raised their hand first to enable a fair order of speakers.

Transparency

In the same way virtual meetings have improved accessibility for patient and public contributors, a notable benefit is the increased access to committee meetings for stakeholders and external audiences.

Virtual meetings are not as restrictive in space when compared to physical meeting rooms, and the removal of cost and time implications associated with travel allows and encourages more public observers to attend. This increased attendance helps to increase the transparency of how evidence is scrutinized and enables more people to observe the decision-making process.

Virtual committees also provided additional opportunities to support future contributors by enabling them to attend and observe a committee meeting prior to their own engagement. This enables external stakeholders and patient and public contributors to better understand the processes, what to expect in their committee meeting, the committee membership, the types of questions asked, and the committee dynamics.

Intrapersonal Relationships and Committee Dynamics

Whilst virtual engagement has brought many benefits, we need to identify and understand the new barriers to meaningful PPI virtual spaces introduce, and develop methods to overcome these. One of these barriers is the restricted opportunity to form interpersonal relationships between committee members. This relationship-building through informal conversations, getting to

know each other, discussing ideas and sharing notes usually takes place before and after the meeting, and during breaks. In virtual spaces this opportunity to speak outside of the formal setting has been significantly reduced, and so measures to include additional informal engagement opportunities are required. For example, for some decision-making committees NICE invites the Chair and lay members to technical engagement calls and to join a virtual break-out room with clinical and patient experts prior to the meeting.

There are also challenges that a virtual setting can reduce the flow of conversations and opportunities to bounce ideas off each other due to the impersonal setting. There is also a distinction in the inability to read people's body language, facial expressions, and non-verbal communication. This can increase the difficulty in gauging reactions.

INNOVATION TWO: DEVELOPING GUIDANCE FOR A HYPOTHETICAL TECHNOLOGY

Another innovative PPI approach during COVID-19 was the requirement to react to an emergence evidence base in real-time. A case study for this was the development of an exploratory hypothetical economic modeling of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral detection point of care tests (13). However, as there was no specific technology being discussed at the time an innovative PPI approach was required to ensure the committee could develop a framework to:

- consider the value of a technology that didn't yet exist for SARS–CoV−2 viral detection point of care tests and serology tests;
- discuss a disease for which the knowledge-base was emerging in real time;
- understand the complex systems into which this innovative technology would be introduced and whether aspects might have the potential to cause additional harm to some demographics in ways that couldn't be incorporated into cost-effectiveness models;
- explore the economic modeling of supporting those developments at scale as well as the potential value to individuals and wider groups.

Two patient experts co-produced patient input for the decision-making committee. They were aware that a hypothetical, reliable, appropriate diagnostic testing would have a substantial role in removing some of the burden of implementation and management for patients, informal carers, and their social networks of support. They felt it would be essential for the functioning of society, from education, and civic involvement to the personal and economic security of much of the population. They anticipated that the long-term consequences of some funding, technical, and social decisions might fall disproportionately on some groups that were already disadvantaged.

Due to the hypothetic nature of the topic, patient experts could not draw on personal experience as no specific test was being discussed. Instead, they explored several health and social care scenarios in which tests might be deployed by drawing on their professional experience and personal caring experience. They used this experience to understand the design requirements, accessibility and usability issues, and issues around trust for introducing novel technologies into complex systems, especially in potentially exigent circumstances. This enabled them to propose outcomes relevant to patients and the public, as well as social and other barriers that reflected responses to similar technologies.

Presenting the expected concerns and potential barriers at an early stage increased the committee's understanding of patient and public needs and desired outcomes, enabling discussions to focus on the impact on those requiring the tests.

> *"I think that our presentation did make the discussion focus on "real people," and how the technology and implementation of it might be perceived by service users. It was difficult to assess how well the issues raised were received, or whether they will make an impact going forward, given the unusual circumstances of the discussions which were based on a hypothetical model in a hypothetical hospital setting."* NICE patient and public committee member

DISCUSSION

The COVID-19 pandemic and lockdown measures in the United Kingdom resulted in significant challenges and created opportunities for innovation to keep patients at the heart of HTA.

NICE introduced rapid, innovative updates to long-established PPI methodologies and adapted these in real-time to ensure they adhered to NICE's patient and public involvement principles (9). The introduction of virtual engagement resulted in many benefits, but it also introduced additional barriers to meaningful involvement. Whilst measures were identified to mitigate the risk of exclusion from the beginning, such as ensuring all committee members were provided training to use the software, other barriers were identified as they came up. This required NICE to embrace a responsive approach to ensure appropriate support and adjustments were able to be identified and introduced in the evolving practice.

Developing guidance for hypothetical situations also demonstrated the benefit of meaningful PPI. Despite the technology not yet being developed, the experience and expertise of the patient experts ensured the committee identified and understood the expected health and social care scenarios. This ensured committee decisions focused on the impact of those requiring the technology, resulting in a framework that addressed the expected concerns and potential barriers for when a technology would be introduced.

The unprecedented lockdown situation was a significant driver for these changes. The legacy of increased inclusivity, accessibility, transparency, and impact should be commended as a positive in the practice of PPI. An additional legacy should be the realization that HTA bodies have access to people who are familiar with some of these drivers and have the experience of using the technology and understanding of the relevant issues. This can assist establishing best practice from the outset. The

culture of reacting quickly to change and embracing novel approaches also needs to be continued and nurtured. By doing so, HTA bodies can continue to strengthen approaches to keeping patients at the heart of HTA.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The article draws on data submitted to the 2021 HTAi conference through a panel discussion. Requests to access these datasets should be directed to mark.rasburn@nice.org.uk.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Patient and Citizen Participation in the Identification of Ethical Considerations Aiming to Address Uncertainty in the Evaluation of Promising Interventions in a Pandemic Context

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Since the beginning of the COVID-19 pandemic, numerous studies have been conducted to identify interventions that could contribute to alleviating the burden it has caused. The Institut national d'excellence en santé et en services sociaux (INESSS) has played a key role in informing the government of Québec regarding the evaluation of specific pandemic-related interventions. This process took place in a context characterized by a sense of urgency to assess and recommend potential interventions that could save lives and reduce the effects of the disease on populations and healthcare systems, which increased the pressure on the regulatory agencies leading these evaluations. While some of the interventions examined were considered promising, results from COVID-19 studies often led to uncertainty regarding their efficacy or safety. Regulatory agencies evaluating the value of promising interventions thus face challenges in deciding whether these should be made available to the population, particularly when assessing their benefit-risk balance. To shed light on these challenges, we identified underlying ethical considerations that can influence such an assessment. A rapid literature review was conducted in February 2021, to identify the main challenges associated with the benefit-risk balance assessment of promising interventions. To reinforce our understanding of the underlying ethical considerations, we initiated a discussion among various social actors involved in critical thinking surrounding the evaluation of promising interventions, including ethicists, clinicians and researchers involved in clinical or public health practice, as well as patients and citizens. This discussion allowed us to create a space for exchange and mutual understanding among these various actors who contributed equally to the identification of ethical considerations. The knowledge and perspectives stemming from the scientific literature and those consulted were integrated in a common reflection on these ethical considerations. This allowed patients and citizens, directly affected by the evaluation of pandemic-related interventions and the resulting social choices, to contribute to

the identification of the relevant ethical considerations. It also allowed for reflection on the responsibilities of the various actors involved in the development, evaluation, and distribution of promising interventions in a setting of urgency and uncertainty, such as that brought about by the COVID-19 pandemic.

Keywords: patient participation, citizen participation, promising interventions, uncertainty, pandemic, COVID-19, benefit-risk assessment

INTRODUCTION

The COVID-19 pandemic has seen an unprecedented mobilization of the scientific community and unparalleled efforts to develop interventions for reducing or countering its impact on individuals and on healthcare systems. These efforts have led to numerous scientific publications aiming to inform regulatory bodies and agencies in their assessments of promising interventions. The body of published scientific evidence often raised more questions than provided answers concerning the benefit-risk balance associated with these interventions. In this context, it appears important to reflect on the conditions under which a promising COVID-19-related intervention can be offered to the population.

In the field of health technology assessment, there is a consensus that recommendations regarding the population's access to promising interventions should be in full compliance with the standards and principles for demonstrating their efficacy and safety, namely the harmonized clinical practices set out by the International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (1). Such recommendations should also be in full compliance with the standards and principles applicable to the assessment of drugs, technologies and interventions in health and social services, including scientific rigor, equity, and the fairness and reasonableness of their use (2). Tensions surrounding the equilibrium required when applying these standards quickly emerged during the pandemic emergency, putting pressure on the social choices to be made. At the center of this situation lies the need to assess the balance between the benefits to the population (e.g., reducing strain on the healthcare system) and the risks to individuals (e.g., adverse events), in a setting of considerable uncertainty regarding the developing body of scientific evidence. It is in this context that the Institut national d'excellence en santé et en services sociaux (INESSS) conducted a reflection aiming to identify ethical considerations that could support the benefit-risk balance assessment of a promising intervention in the context of a pandemic. INESSS's mission focuses on the assessment of drugs, technologies and interventions in healthcare or social services. For this reason, "promising interventions" in this article include drug treatments and healthcare interventions provided to individuals being treated for COVID-19 disease. They do not concern vaccines or public health measures deployed to contain the pandemic.

The aforementioned reflection was initiated near the beginning of the COVID-19 pandemic, with the publication of a first "rapid response" in April 2020 regarding access to promising treatments and interventions in the pandemic context (3). This was followed by the publication, in June 2021, of a second rapid response regarding ethical considerations relevant to the assessment of the benefit-risk balance of promising interventions, entitled "Les fondements éthiques de l'évaluation de l'équilibre bénéfices-risques d'un traitement prometteur en contexte de pandémie" (4). In the present article, we push this work forward and examine the process by which the latter rapid response was produced, and the challenges raised when generating scientific evidence, evaluating promising interventions and assessing their benefit-risk balance in a pandemic context. We also explore the ethical considerations that can facilitate such an assessment, focusing on contributions to the reflection by patients and citizens. As pandemics evolve and novel pathogens and variants emerge around the globe, the need for promising interventions will continue to put pressure on the social choices to be made regarding their access, making it even more urgent to include ethical considerations stemming from various actors, including patients and citizens, in the assessment process.

In addition to considering the clinical dimension of promising interventions, the benefit-risk balance considers all the societal benefits and risks associated with the populational, sociocultural, organizational, and economic aspects regarding access to promising interventions. While presenting the major challenges identified in the scientific literature and the initiatives put forward by some regulatory agencies, this article mainly focuses on the various perspectives that were expressed in discussions that brought together ethicists, clinicians and researchers involved in clinical or public health practice, as well as patients and citizens affected by health issues related to the pandemic. It specifically aims to illustrate the crucial role played by patients and citizens as participants in the reflection and emphasizes their influence on the identification of ethical considerations aiming to address uncertainty in the assessment of the benefit-risk balance of promising interventions.

METHODS

The reflection included an initial rapid literature review that allowed exploration of the challenges identified, related to generating scientific evidence in a pandemic context and assessing the benefit-risk balance of promising interventions. This literature review served as the basis for the discussions held with the various social actors affected by the evaluation of pandemic-related interventions and decision-making on their access by the population.

Literature Review

Search for Publications

For the purposes of this discussion, a strategy was developed in February 2021, in collaboration with an information specialist, to search for articles on the assessment of benefits and risks associated with promising interventions in a pandemic context, published in English or French since 2015 (**Appendix A**). The publication year limit was set as 2015 to cover discussions from the most recent epidemics, including those involving the Middle East respiratory syndrome coronavirus and the Ebola virus. The MEDLINE database and the Google and Google Scholar search engines were searched using keywords, which included the following: pandemic; epidemic; outbreak; benefit-risk evaluation; promising; new drug; drug use; intervention; responsibility; solidarity; justice; benefit-sharing; burden-sharing; equity; fairness; minimization of risks; maximization of benefits; unmet needs; integrity; harm reduction; beneficence; resource allocation; statistical significance; clinical significance. In October 2021, this strategy was renewed, focusing on articles published after February 2021 in order to capture the most recent literature. The websites of Health Canada, the U.S. Food and Drug Administration, and the European Medicines Agency were also searched in May 2021 to identify the main guidelines developed for evaluating promising interventions during the COVID-19 pandemic. In addition, a search for similar articles based on the studies by Califf et al. (5) and Ogburn (6) was conducted in PubMed. The search strategy yielded one pertinent reference from 2014, which was also included in the review.

Publication Selection

The initial search yielded 995 articles, which were examined by a single reviewer due to human resource and time constraints. The analysis of the titles and abstracts resulted in the selection of 62 articles possibly relevant to the topic of the benefits and risks associated with promising interventions in a pandemic context. The retained publications included reviews, commentaries, editorials, qualitative research and ethics articles. Documents not dealing with the benefit-risk assessment of interventions were excluded. Thirty-four articles were then read by the single reviewer. Documents concerning the analysis of the benefits and risks of a specific intervention were excluded to focus the extraction on a more general discussion concerning benefit-risk balance assessment. The second search yielded 1,677 articles from which 5 publications were selected after the application of our inclusion criteria. A total of 25 articles were included in our final literature review.

Data Extraction and Synthesis

Data extraction was carried out on the 25 articles by a single reviewer due to human resource and time constraints. Extraction aimed to identify the various pieces of information and positions in the literature regarding the challenges, limitations and issues associated with the benefit-risk assessment of promising interventions and its underlying considerations.

Consultation Process

Group Discussions

Two group discussions were held to gain more specific insight into the experience of assessing the benefit-risk balance of promising interventions in Québec during the COVID-19 pandemic. The objectives of these group discussions were to more clearly understand the influence that the pandemic context can have on assessment activities and to provide INESSS with information about the considerations that could be proposed for assessing the benefit-risk balance of promising interventions.

The first group discussion aimed at bringing together and exchanging on the perspectives of research ethics boards, scientific evaluation committees, peer review committees that adjudicate the results of the numerous research projects underway on promising interventions, and patients and citizens directly affected by the social choices involved. Participants were selected through purposeful sampling and network sampling. Experts were recruited by personal invitation. Citizens were recruited through a call for participation to those serving on INESSS's advisory committees, in order to promote diversity of opinion on the topic. Lastly, a patient coordinator from the Methodology and Ethics Office with keen interest in ethical issues also participated in the discussion and was involved in recruiting a person who had developed COVID-19 disease in the previous year. A total of 13 people participated in a discussion held in February 2021, including ethicists, clinicians, a pharmacist, researchers, patients and citizens.

The second group discussion aimed at increasing understanding of the patient's perspective concerning the assessment of pandemic-related interventions and the conditions for their access by the population. This group discussion involved members of the Citizen Partners Committee of the Center of Excellence on Patient and Public Partnership (CEPPP), a committee made up of patient partners and caregivers who have an interest in and have taken a position on various topics pertaining to the COVID-19 pandemic. A professional scientist, a medical consultant and a patient coordinator from the Methodology and Ethics Office met with 13 members of the CEPPP committee during one of its regular meetings in March 2021.

Both meetings were recorded with the attendees' consent, and notes were taken. The notes were supplemented by the recordings. The consultations were rapidly analyzed to identify the main themes identified by the participants and the observations and positions relevant to the discussion. This analysis revealed the challenges and limitations of generating evidence and of assessing the benefit-risk balance of promising interventions encountered during the COVID-19 pandemic. It also identified some issues and considerations that might be important for the benefit-risk assessment of promising interventions.

Participants were selected for their particular interest in the topic. Conflicts of interest and roles were declared and disclosed in accordance with the *Politique de prévention, d'identification, d'évaluation et de gestion des conflits d'intérêts et de rôles des collaborateurs de l'INESSS* (Policy for the Prevention,

Identification, Evaluation and Management of Conflicts of Interest and Roles of INESSS Collaborators). Nine participants from the February 2021 consultation declared having been involved in at least one committee involved in COVID-19 healthcare organization or decision-making, or an evaluation committee at INESSS before taking part in our consultation. Furthermore, 10 members of the Citizen Partners Committee reported serving on at least one committee concerned with COVID-19, such as a committee on health technology utilization, mental health, medications or the impact of COVID-19 on immunocompromised individuals, or on a health policy group associated with the Fonds de recherche du Québec. One person reported serving on a committee led by Pfizer on a topic other than COVID-19.

Participants at the February 2021 consultation served as external reviewers of the second rapid response published by INESSS to ensure that the reported perspectives accurately reflected the discussions held. The results of the two group discussions are reported herein and integrated within the current reflection, complementing the findings from the scientific literature.

STATE OF KNOWLEDGE AND ACTORS' PERSPECTIVES ON THE CHALLENGES IN THE ASSESSMENT OF PROMISING INTERVENTIONS

This section first presents the challenges of generating evidence in a pandemic context, particularly regarding the efficacy and safety of promising interventions. It then presents the challenges this situation poses for assessing their benefit-risk balance.

Challenges of Generating Evidence in a Pandemic Context

According to the literature, only a few promising interventions were approved or recommended during previous pandemics (7). Various factors have been identified to explain this low approval rate. Most of these have to do with the context in which research is conducted during a pandemic and pose challenges for generating sound scientific evidence concerning the efficacy and safety of interventions, rendering it difficult to assess their benefit-risk balance. These challenges result from the influence that the context has on the methodological designs of the clinical trials, and from the limitations they impose on the quality of the evidence produced.

Influence of the Context on Methodological Design

The factors that can influence methodological design include the rapidity with which studies are conducted, time and participant recruitment constraints, and a lack of organization and coordination to allow for quick launching of pertinent research projects (8–10).

The sense of urgency and the generally short but intense duration of pandemics can explain the desire of the scientific community to promptly provide effective interventions to the population. In such a context, trials are often carried out quickly, which can lead research teams to propose methodological changes that depart from usual clinical research practices (9). Specifically, trials might be conducted without a control group and might involve the administration of concomitant interventions, which is likely to yield only a suboptimal estimate of their efficacy or safety (9). In addition, long-term trials are difficult to conduct during a pandemic, which forces research teams to adopt methodological designs that take the time constraint into account.

The emergency context can also influence the size of the cohorts included in the trials. On the one hand, the number of people who can participate in the clinical trials varies according to the course of the pandemic. For example, the ending of a pandemic can cause trials to stop before clear efficacy or safety results on the interventions are obtained (11). On the other hand, this context makes participant recruitment difficult, resulting in many studies being conducted with cohorts that are too small to obtain meaningful results representative of the clinical reality (8). The experts that took part in our consultation mentioned that the risk of over-soliciting COVID-19 disease positive individuals made participant recruitment difficult during the COVID-19 pandemic. They also stressed that some institutions imposed exclusivity with respect to specific research projects on themselves, limiting the recruitment of participants for other research projects. They argue that these challenges highlighted the need to centralize participant recruitment and to better coordinate their allocation to the various ongoing trials, at least at the organizational level.

Participant over-solicitation and the need for coordination of research projects conducted in a pandemic context at the national and international level are also identified in the literature as major issues that can influence the quality of the methodological design of clinical trials. Franks et al. showed in their study that there has been an increasing misalignment between the location of trial sites and COVID-19 geographic incidence, demonstrating the importance of coordinating pandemic research efforts (12). In view of these issues, Meyer et al. propose that a system for prioritizing research projects should be established to identify the highest-quality projects, i.e., those that permit a certain complementarity in terms of target populations and types of intervention (13). The implementation of such a system could help foster equity in the development and delivery of promising interventions for population groups in vulnerable situations in a pandemic setting (14).

The challenges associated with the course of the pandemic, participant recruitment, and research project coordination can result in changes to the methodological design of clinical trials and reduce the pool of participants available for research, rendering it difficult to obtain sufficiently clear results in a timely manner. As a solution, Dean et al. suggest using core protocols to study the use of multiple interventions for the same disease or the use of one intervention for multiple diseases simultaneously, to increase the likelihood of obtaining clear evidence (10). Others describe the importance of shared infrastructure to increase trial efficiency and reduce the threat to the scientific rigor that may arise in a context of urgency (15). Adaptive trial initiatives such as the REMAP-CAP platform and the RECOVERY and

SOLIDARITY trials are excellent examples. The REMAP-CAP platform is an international initiative launched in 2019 that includes multiple sites in Europe, Australia, New Zealand and Canada and whose goal is to determine the efficacy of various interventions in reducing mortality in patients with severe community-acquired pneumonia (16), while the RECOVERY trials, a British initiative, and SOLIDARITY, a World Health Organization (WHO)-led initiative, were launched during the COVID-19 pandemic (17). Among other results, these initiatives have led to a certain level of coordination in recruitment, randomization, and trial prioritization.

Limitations to the Quality of the Evidence

The greatest challenges for trials conducted in a pandemic context appear, however, to have to do with demonstrating the real efficacy and safety of interventions (5). Although many publications have suggested that some of the interventions being investigated have potential benefits in treating COVID-19 disease, it has been difficult to make a clear ruling about their actual efficacy based on clinical trials involving larger cohorts (18). This situation is far from unique to the COVID-19 pandemic, having also been confirmed during the recent Ebola, Zika, and Severe acute respiratory syndrome epidemics (7).

In addition to the difficulties encountered in demonstrating the efficacy of promising interventions, it has been found that many of the COVID-19 interventions undergoing trials are accompanied by adverse effects significant enough to call their safety into question (19). In particular, uncertainty regarding the efficacy and safety of the interventions may have led regulatory agencies to recommend against their use outside of a clinical trial or to limit their use to certain situations, as the World Health Organization (WHO) and INESSS have done. Yet, it can be complicated for research teams to distinguish between adverse events that result from the course of the patient's disease and those related to the intervention (20, 21). In the context of COVID-19, the care pathway, the presence of comorbidities, and the stage of the disease all appear to be determinants of patient survival or death (21). Sex and gender also seem to influence patient mortality and individual response to the promising interventions. However, according to Brady et al. COVID-19 clinical trials have rarely taken these factors into consideration, undermining the generalizability of their results (22). In addition, safety data on promising interventions undergoing trials are sometimes missing from publications or registries, which limits their dissemination within the scientific community (2). In this context, Bhatt recommends that research ethics boards conduct an ongoing assessment of the benefit-risk balance of the different clinical trials underway (23).

The experts consulted also stressed the potential benefit of obtaining umbrella ethics approval, i.e., authorizing the conduct of multiple clinical trials for an intervention in several diseases that have similar effects on patients, such as respiratory diseases, so that trials can be launched more quickly if a pandemic emerges. In this regard, Dean et al. suggest that, despite the ending of a pandemic, it is not desirable to shut down related research projects, but rather keep them active so that they can restart quickly when an epidemic involving the same infectious agent re-emerges. To do this, they note the importance of having an independent data monitoring committee to monitor research and make recommendations relating thereto (10). Groβhennig and Koch point out that early termination of clinical trials is likely to make their evaluation by responsible organizations and agencies more challenging (24). Like Dean et al., they note the importance of relying on the recommendations of an independent data monitoring committee to support informed decision-making about shutting down projects. In the Canadian context, the need for independent monitoring committees is also mentioned in the Tri-Council Policy Statement (TCPS2). To be considered independent, this committee should normally have little or no particular interest in the research underway, the manufacturer or the research team, nor administrative responsibilities within the institution hosting the research, to prevent situations of actual, potential or perceived conflicts of interest (25).

The challenges of clearly demonstrating efficacy and identifying adverse effects attributable to the interventions can influence the quality of clinical trial evidence. This makes it very complex to assess the benefit-risk balance of the various interventions, including assessing the potential impact of introducing them into clinical practice (6).

The Challenges of Evaluating Promising Interventions

In response to the sense of urgency that accompanies pandemics, regulatory agencies are proposing evaluation and authorization mechanisms aimed at ensuring speedier access to promising interventions by the population. Some of these mechanisms are described in INESSS's April 2020 rapid response and precede the COVID-19 pandemic. Several regulatory agencies have instituted such mechanisms during the COVID-19 pandemic or have developed specific guidelines for evaluating promising COVID-19 interventions. For example, as early as April 2020, the U.S. Food and Drug Administration (FDA) announced its emergency program, CTAP (Coronavirus Intervention Acceleration Program), for expediting the evaluation of promising COVID-19 interventions. The FDA states that it is using all available means to conduct evaluations and plans to continuously evaluate intervention data as the results from ongoing clinical trials are released. At the time the present article was submitted for publication, ∼470 clinical trials had been evaluated through this program, which has resulted in 11 interventions being authorized for access through the emergency use program, and one being approved for unrestricted use in COVID-19 disease (26).

The European Medicines Agency (EMA) adopted similar initiatives to those of the FDA to support the development of promising COVID-19 interventions and accelerate their evaluation procedures (27). These initiatives stem from a plan to manage emerging health hazards that the agency adopted in 2018 (28). For its part, Health Canada adopted interim orders to expedite the approval of drugs, vaccines and medical devices related to management of COVID-19 in Canada, as well as to regulate COVID-19 drugs sale and importation (29–31). Certain

key elements stemming from these interim orders have now been officialized by the adoption of the Regulations Amending Certain Regulations Concerning Drugs and Medical Devices (Shortages), published in September 2021 (32). Regulatory agencies are thus contributing to disseminating efficacy and safety data on promising interventions sent to them for the purpose of their ongoing evaluation processes.

Applying these various mechanisms and guidelines nevertheless requires an evaluation of the efficacy and safety of promising interventions, which is subject to the challenges identified in generating evidence in a pandemic context, particularly regarding benefit-risk balance assessment. In addition, the nature of the outcomes measured, the relevance of the cohorts selected in relation to the intent of the interventions, and the choice of analyses performed can all contribute to rendering this evaluation difficult.

Challenges of Benefit-Risk Balance Assessment

Assessing the benefit-risk balance of promising interventions is a necessary step in decision-making regarding their access by the population (33). This assessment is distinct from the evaluation carried out by research ethics boards when approving the conduct of projects. Indeed, the considerations differ when going from evaluating the expected benefits and the potential risks for the participants in a controlled research setting to that of assessing the reasonably expected benefits and actual risks incurred for the population. Those responsible for making this assessment therefore must navigate through the uncertainty surrounding the evidence from clinical trials conducted during the pandemic emergency.

Reconciling the considerations concerning the acceptable benefit-risk balance for the population in general, and for individuals according to their particular situation, can prove to be exceedingly complex in the context of a health emergency, especially if the individual benefits or risks appear small while the public health benefits or risks appear significant, or vice versa (14). The media attention that sometimes accompanies intervention assessment processes and the scientific community's culture, which favors siloed scientific production, are also factors that can influence individual and social perceptions concerning the recommendations for or against access to promising interventions (8). All these factors are likely to make the benefit-risk balance assessment difficult for the evaluation team. The experts consulted reported having encountered such pressures during the evaluation of certain promising COVID-19 interventions, especially concerning their potential impact on the course of the pandemic.

During the COVID-19 pandemic emergency, many of the interventions being tested were previously approved for other disorders or diseases. The perceived advantage of testing pre-existing interventions is that they have already been shown to be safe in a clinical research setting. However, it is still important to assess all the safety parameters of interventions in the particular setting of the current pandemic, including specific responses to the infectious agent and interactions with any concomitant intervention (33). Penman et al. stressed the importance of assessing the benefit-risk balance of a given intervention before considering its use for COVID-19, especially if it is an intervention for preventing infections. In addition, Bellera et al. point out that it cannot be assumed from the prior safety demonstration of an intervention being evaluated for repurposing that it has an acceptable benefit-risk balance for the intended populations (34). Furthermore, the safety demonstration of an intervention can evolve in light of new results. Those who evaluate promising interventions can therefore face significant uncertainty regarding their benefit-risk balance. Some experts that took part in our consultations clearly expressed a preference for not granting access to an intervention when in the presence of such uncertainty.

Patient and citizen perspectives

Among the patients that took part in our consultations, some who felt more susceptible to the potential adverse effects of interventions for which there remains uncertainty expressed a preference for applying the precautionary principle in their personal decision-making, to avoid exposing themselves to risks. However, these positions were mitigated by those of other participants in the consultations, as the following discussion demonstrates.

Our consultations thus highlighted the importance of shared responsibility in decision-making regarding access to promising interventions. Indeed, the uncertainty stemming from the efficacy and safety data of an intervention is in tension with patients' health needs, but also with those of the general population in this context. The considerations specific to the respective responsibilities borne by the different stakeholders in this regard appear to be key elements in the discussion of the interventions' benefit-risk balance, particularly with respect to the resulting individual vs. populational responsibilities.

Individual Responsibility

The assessment of what constitutes an acceptable benefit-risk balance varies from one individual to another and according to the context in which the person finds herself (e.g., life stage, the presence of comorbidities, and a predisposition to risks) (33). Papadimos et al. argue that this assessment is value-laden and should, at the individual level, respect the patient's own values and priorities.

Regarding this question, Li et al. surveyed COVID-19 patients about their preference for obtaining standard care, participating in a randomized clinical trial or having immediate access to a promising intervention (35). Their results show that most of those surveyed with mild or moderate COVID-19 disease would prefer to participate in a randomized trial of a promising intervention, while those with severe disease would prefer to have direct access to the promising intervention.

Patient and citizen perspectives

The patients consulted for the purpose of this reflection also indicated that the form of the disease could influence their eagerness to have prompt access to a promising intervention. Most of these patients expressed their support for prioritizing

knowledge building about promising interventions through research. However, they said that for some people with a severe or very severe form of the disease, it might be preferable to have access to these interventions without having to participate in a research project, even if there is no clear demonstration of an acceptable benefit-risk balance to justify such access. Similarly, these patients were of the opinion that people with a high-risk profile for developing serious complications of the disease should have the possibility of direct access to promising interventions. This would not necessarily be the case for people with few or no symptoms.

During both consultations, the patients and citizens expressed a position strongly in favor of individual responsibility for assessing the benefit-risk balance of promising interventions. In their view, this responsibility takes the form of a shared decision between clinicians and patients and the expression of the latter's free and informed consent. In this sense, they believe that it is essential to respect the patient's choice regarding the possibility of receiving a promising intervention, while ensuring that they are provided with all the information necessary for understanding the uncertainty about the benefits and risks that this might entail. The patients and citizens confirmed that the expression of a position in favor of an intervention by bodies or agencies responsible for its evaluation can increase the level of trust in these interventions. However, these persons felt that a favorable position would not prevent them from making a free and informed decision about them.

The experts consulted agreed on the importance of respecting individual patient choice for interventions that have been approved for clinical use by regulatory bodies or agencies.

Populational Responsibility

The preceding discussion therefore raises the question of responsibility for the benefit-risk assessment of promising interventions for the population more generally. This populational responsibility is held by various actors (e.g., researchers, manufacturers, HTA and regulatory agencies, and governmental bodies) integrity and social consciousness to ensure that the choices made concerning access to promising interventions are well-reasoned. The emergence of a pandemic creates a sense of urgency for developing interventions, in the first instance to save as many lives as possible, but also to reduce strain on the population and healthcare systems.

Thus, when there is a lack of evidence from randomized clinical trials to inform decision-making regarding promising interventions, regulatory bodies and agencies have sometimes had to rely on other types of data to make recommendations about which clinical practices to endorse (6). According to Ogburn, this may have led to opaque decision-making, which is subject to influence by political and media pressure surrounding the pandemic. The need for greater transparency in communicating the benefits and risks associated with decisions made to reduce the impact of the pandemic on the population was also raised during our consultations. To be responsible, this transparency should not be subject to such media or political pressure.

Indeed, some manufacturers and research teams conducting research on interventions previously approved for other disorders or diseases have used the media space or arenas reserved for scientific prepublication to promote the potential benefits and expected low risks of the interventions on which they work. Although this has resulted in faster sharing of research results, such information has sometimes been disseminated prematurely, which could have influenced the public's perception of an intervention's benefit-risk balance and increased pressure on the teams responsible for its assessment (19). Furthermore, a meta-analysis published by Bellos suggests that COVID-19 intervention research is susceptible to "white hat bias," leading to greater reporting and more citations of positive vs. negative effects of promising interventions within the scientific realm (36). He argues that this type of bias may have contributed to propagating beneficial over neutral or harmful outcomes and increased the risk of creating medical misinformation concerning pandemic-related interventions of uncertain effect.

In this regard, the Council for International Organizations of Medical Sciences (CIOMS) states that in order to be considered ethical, research must have social value. In other words, it must demonstrate the relevance and reliability of the information it can generate (37). Generating information from projects with social value is considered an important step for informing access-to-intervention decision-making in an emergency context. However, prematurely disseminating information about promising interventions can influence the public's perception of their relevance and reliability, which makes informed decision-making difficult. CIOMS also mentions the risks associated with conflict between the interests of manufacturers or research teams and those of communities that access-to-intervention decisions can entail, particularly when it comes to ensuring fair and equitable allocation of limited health resources.

Buruk et al. analyzed both WHO's International Clinical Trials Registry platform and clinicaltrials.gov to verify whether the registered COVID-19 trials included information regarding various ethical criteria, including study design, conflicts of interest, enrollment of healthcare workers, and participant-related issues (38). They found that most registered studies showed inconsistencies regarding trial phases and lacked information on conflicts of interest. The effect that prematurely disseminating information can have and the risk of conflicts of interest that can emerge from research seem to be elements to consider for ensuring responsible decision-making for the population. With this in mind, the consulted experts said that in the absence of sound evidence on the efficacy and safety of a given intervention, it would be best to continue research on it. On the other hand, they noted that the issue could be viewed differently if research is not available to the population. The decision to limit access to promising interventions to the research setting until clear evidence is obtained should therefore be based on the possibility of actual access to such research.

The fact that many of the promising interventions being tested are already approved and used to treat other disorders or diseases

has also had a detrimental impact on their allocation. Among other outcomes, this has led to a risk of shortages of or restricted access to some of the repurposed interventions (6, 9, 14). It therefore appears that the use of such interventions can have consequences for others in the population and thus can create an unanticipated populational risk that should be considered.

According to the experts consulted, a prioritization and coordination mechanism must be put in place to manage the supply of promising interventions once they have been approved and to reduce undesired impact on various groups. Furthermore, the approval of new interventions or the repurposing of promising ones require the assurance that the supply system has sufficient capacity to produce them, given that their use is to be recommended in the context of a pandemic. If there is no such assurance, initiating a transparent access prioritization exercise will be required, as well as proposing alternatives to the interventions concerned, if deemed necessary.

ETHICAL CONSIDERATIONS TO SUPPORT BENEFIT-RISK BALANCE ASSESSMENT

Based on our literature review and the consultations conducted for the purpose of this reflection we are able to identify considerations that may be useful to bear in mind when evaluating promising interventions. Although the benefit-risk balance is often associated with the clinical aspects of interventions, it quickly became apparent that the considerations identified concern different dimensions of the assessment process and require an assessment of their global value. These considerations are presented below while exploring the dimensions used to assess the global value of interventions at INESSS, namely, the clinical, populational, sociocultural, organizational and economic aspects (39).

Clinical Considerations

One of the first considerations raised during the consultations was the influence that the severity of the disease can have on the pandemic emergency. It was suggested that a high mortality rate in the infected population (e.g., as with Ebola), coupled with the rapid spread of the disease, can foster the perception that the urgency of the situation justifies greater tolerance of risks or uncertainty regarding a promising intervention.

Furthermore, the clinical severity of the disease can vary, depending on the individual's profile. The characteristics that define such a profile include, among others, the form of the disease (mild, moderate or severe), the individual's overall health status (presence of comorbidities, stage of the disease, predisposition to complications), the care trajectory (pre-hospitalization, hospitalization, use of mechanical ventilation), and the intent of the promising intervention (a reduction in symptoms, in hospitalization, in the use of mechanical ventilation, or of mortality). In this regard, Penman et al. propose that it might be acceptable to expose patients with severe late-stage COVID-19 disease to a given intervention, whereas this would not be acceptable at all to patients with a mild or moderate form of the disease (33). The benefit-risk balance of access to promising interventions could thus vary according to the patient's profile. Nevertheless, the consulted experts stated that to consider access to an intervention acceptable, it cannot carry risks exceeding those that the disease itself poses.

Patient and citizen perspectives

The patients and citizens consulted spoke of the importance of taking into consideration an individual's willingness to accept a certain amount of risk with regards to the interventions that might be required in an emergency. This position highlights the dilemma that can arise between populational considerations in a public health emergency and individual considerations in an emergency care situation in the context of a pandemic. The differences identified in the clinical profiles that people might have can influence the perception of the benefit-risk balance of using a promising intervention for which efficacy or safety is uncertain.

The patients and citizens also indicated that some of the characteristics identified justify the idea that decisional responsibility for using a promising intervention should be borne by the individual (i.e., individual responsibility). These characteristics include, in particular, having a severe form of the disease, being hospitalized and potentially requiring the use of mechanical ventilation, having comorbidities or a predisposition to severe complications, and receiving an intervention intended to reduce the need to use mechanical ventilation or decrease mortality.

The discussion between the experts, patients and citizens allowed for the identification of the characteristics that can shift the decision regarding access to promising interventions toward a populational or organizational responsibility, such as facing a mild or moderate form of the disease, not needing hospitalization, the absence of risk factors for complications of the disease, and using an intervention intended to prevent hospitalization or reduce pre-hospitalization symptoms. Furthermore, the social context and the populational emergency that characterizes the pandemic can also influence the level of responsibility involved. It therefore seems that responsibility for these issues might reside at different levels, depending on the individual or populational priorities. Still, the responsibility for managing a pandemic lies primarily with the various policy-making bodies, such as healthcare facilities, health ministries, and regulatory bodies and agencies.

Populational Considerations

One important consideration is the need to reduce the strain that a pandemic puts on the population and the healthcare system. It appears that regulations concerning access to promising interventions can have a negative impact on certain population groups or the healthcare system itself. This is particularly the case when one considers that few clinical trials have focused on the needs of vulnerable groups in the population, such as children or pregnant women (38). In addition, the risk of supply shortages associated with certain promising interventions for COVID-19 disease has illustrated the pressure that can occur in this regard in a pandemic context, particularly regarding the treatment of chronic diseases or other acute care situations. In

response to this risk, Health Canada adopted an interim order on November 27, 2020 concerning drug shortages to safeguard the supply of medications.[1] This order was intended, in part, to respond to the U.S. Department of Health and Human Services' September 2020 Importation of Prescription Drugs Final Rule, which was intended to facilitate the importation of interventions from Canada.

Edwards points out that overly restrictive regulations regarding the use of repurposed interventions can result in these being given or prescribed without their efficacy and safety being monitored (40). This is especially likely to occur with over-the-counter medications and can contribute significantly to creating a shortage of such drugs (9, 40).

Patient and citizen perspectives

In this regard, the patients and citizens we consulted agreed with the experts that prescribing or providing access to promising interventions that are used to treat other disorders or diseases requires a value judgment about the impact this practice can have at the population level.

Indeed, the shortages for certain treatments or interventions that this can cause in the population raise justice and equity issues regarding the allocation of healthcare resources (9).

Sociocultural Considerations

The interventions of interest must demonstrate real added value to justify proposing their use. Alexander et al. point out that interventions must be proven effective and safe based on evidence from rigorous clinical trials validated by an equally rigorous peer review process (9). They believe this to be an essential condition for informed decision-making and that the circumstances of the pandemic emergency cannot transform flawed data into robust results. In May 2021, the International Coalition of Medicines Regulatory Authorities (ICMRA), an international coalition of regulatory bodies from 30 countries including Canada, reaffirmed the importance of being able to verify the integrity of clinical trials data to ensure regulatory decisions will not adversely affect patients using the medicines. For this to occur, they argue that "data must be robust, exhaustive and verifiable, through peer review" (41).

For their part, the consulted experts stated that efficacy and safety demonstrations spelling out the uncertainty associated with the interventions are required for one to be able to make informed decisions about them, both at the populational and the individual level. However, both the literature and our consultations suggest applying this precautionary principle in decision-making regarding access to interventions can also entail risks for the population, having a possible paralyzing effect on the development of promising interventions.

Patient and citizen perspectives

Similarly, to the experts consulted, the patients and citizens that participated in our consultations suggested that, while applying the precautionary principle is warranted in some contexts, it might be useful to remain more agile and open to revising decisions that have been made in order to permit an ongoing evaluation of an intervention's public health benefits. This evaluation may require gathering and evaluating data in real-world care settings, at least with respect to observational data that can support the benefit-risk balance assessment in care settings.

One of the experts consulted added that in such cases decision-making should remain a shared choice between clinicians and patients so as not to paralyze public health programs.

Organizational Considerations

It seems crucial to examine the capacity of policy-making bodies and the healthcare system to deal with different levels of priorities during a pandemic emergency. Indeed, the recommendations made regarding access to promising interventions should consider the feasibility and ability of the healthcare system's actors and its organizational capacity to implement them. In this regard, decision-making should be aimed at streamlining the processes for implementing the recommendations at a time when healthcare institutions are sometimes overwhelmed by the pandemic's impact.

Patient and citizen perspectives

The patients and citizens consulted agreed with the experts who participated in our discussions and suggested that the unusual context of pandemics warrants considering the exceptional nature of the situation when assessing and making decisions about access to promising interventions for the population and for individuals, depending on the situation in which they find themselves.

Economic Considerations

Pandemics can have significant impact on a population's health, the economy and the social context. The COVID-19 pandemic has shown the extent of political, social and economic decisions that are required for its management. The emergency caused by this situation is likely to increase pressure to evaluate and provide access to interventions that seem promising. However, the scientific literature mentions the potential downside of investing in research or rolling out interventions whose efficacy and safety cannot be clearly demonstrated (8, 13). It also mentions that it may be inefficient to invest in expensive interventions that do not show any benefit in terms of reducing the number of hospitalizations, ICU time, or patient mortality.

In this regard, the consulted experts pointed out that interventions can sometimes provide limited benefit to patients, reducing the length of hospital stay only to a small degree or even proving to be toxic. It is therefore not clear that the cost of certain interventions is justified by the level of benefit. However, McCaw et al. note that reducing the length of hospital stay is not an indicator of the actual benefits that promising interventions can provide, which can lead to an under- or overestimation of out-of-hospital survival (42). This decision-making therefore requires a global assessment of the economic issues at play in a

[1]The Interim Order Respecting Drug Shortages (Safeguarding the Drug Supply). Available online at: https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/importation-exportation/interim-order-drug-shortages-protecting-supply/guidance.html (accessed May 26, 2021).

given situation. The sharing of the budgetary burden between the levels of government (national, provincial and municipal) and between the various stakeholders stands out as one of the economic issues particularly important to discuss in a pandemic context.

APPLYING ETHICAL CONSIDERATIONS TO THE BENEFIT-RISK BALANCE ASSESSMENT

To facilitate the benefit-risk balance assessment of promising interventions, it might be useful to draw on existing models of decision-making regarding access to care or to interventions in a context of uncertainty or limited resources or in rare situations. The McGill University Health Center has developed a model that proposes integrating casuistic considerations, i.e., those rooted in a conceptualization of specific cases or contexts, into an organizational decision-making process aimed at making fair and reasonable decisions based on distributive justice considerations [(43), personal communication]. Such a model can be used to assess the benefit-risk balance by considering the above-mentioned characteristics of personal profiles, but also the populational context and the potential impact of intervention access, the priorities that emerge regarding the interventions, and the organizational capacity to manage the conditions of access and the related economic issues.

The benefit-risk balance could thus be described as a variable that depends on the combination of the considerations that have been identified. The integration of the perspectives from the various social actors consulted within this present reflection allowed for better understanding of the ethical considerations that can help address the uncertainty surrounding promising interventions and the proposal of an assessment approach that is sensitive to these considerations. In its 2021 rapid response, INESSS presented four situational profiles for the purpose of supporting benefit-risk balance assessments using the identified considerations (**Figure 1**). It should be noted that these profiles are not intended to describe all the possible combinations of the identified characteristics and considerations, but rather to provide a general framework to support the teams responsible for assessing the benefit-risk balance of promising interventions.

Profile 1 Can Occur in a Situation Where Individual Benefit and Risk Are Expected to Be High and Populational Risk Low

This profile can occur when facing individuals with a severe form of the disease, requiring hospitalization and the use of mechanical ventilation, who have comorbidities or a predisposition to severe complications, or for whom the intervention considered is intended to reduce the use of mechanical ventilation or mortality. Based on the consultations, this profile would allow considering greater individual risk taking despite the uncertainty regarding the interventions' efficacy and safety. The decision-making process concerning access to such interventions could rest on the individual patient concerned and engage the shared responsibility of the clinician in a free and informed consent process. However, to be acceptable from a populational standpoint, access to the promising interventions should not have an adverse impact on the rest of the population (e.g., a shortage that could cause significant harm to other patients). Such access should be easily implementable in the healthcare setting and show sufficient benefit relative to its budgetary impact on the healthcare system or on individuals. In such a case, populational, organizational and economic impact should be among the considerations taken into account by regulatory agencies before allowing individual decisions to be made.

Profile 2 Can Occur in a Situation Where Populational Benefit Is Expected to Be Moderate and Populational Risk Low to Moderate

This profile can occur when facing individuals with a moderate form of the disease, requiring hospitalization without the use of mechanical ventilation, who have comorbidities or a predisposition to severe complications, and for whom the intervention considered is intended to reduce the length of hospital stay, the use of mechanical ventilation or mortality. Given the clinical profile of those who might benefit from the interventions under such a scenario, this profile can be considered to hold promise of a moderate populational benefit. This profile might justify calculated risk taking by patients and clinicians. The decision-making process concerning access to the interventions under this scenario could rest more on shared responsibility between clinicians and patients and requires a situationally proportionate assessment of the benefits and risks as part of the free and informed consent process. However, to be acceptable from a populational standpoint, access to promising interventions should not have an adverse impact on the rest of the population (e.g., a shortage that could cause harm to other patients). Such access should be easily implementable in the care setting and show sufficient benefit relative to its budgetary impact on the healthcare system or on individuals. In such a case, populational, organizational and economic impacts should be among the considerations taken into account by regulatory agencies before allowing shared decision-making between clinicians and patients.

Profile 3 Can Occur in a Situation Where Individual Benefit Is Expected to Be Moderate and Populational Risk Moderate to High

This profile can occur when facing individuals with a moderate form of the disease, requiring hospitalization, who have no comorbidities or predisposition to severe complications, and for whom the intervention considered is intended to reduce symptoms or the length of hospital stay. Furthermore, access to the intervention concerned is likely to create a shortage for other groups in the population. This profile does not justify taking risks concerning the uncertainty associated with the efficacy and safety of the intervention, that could exceed

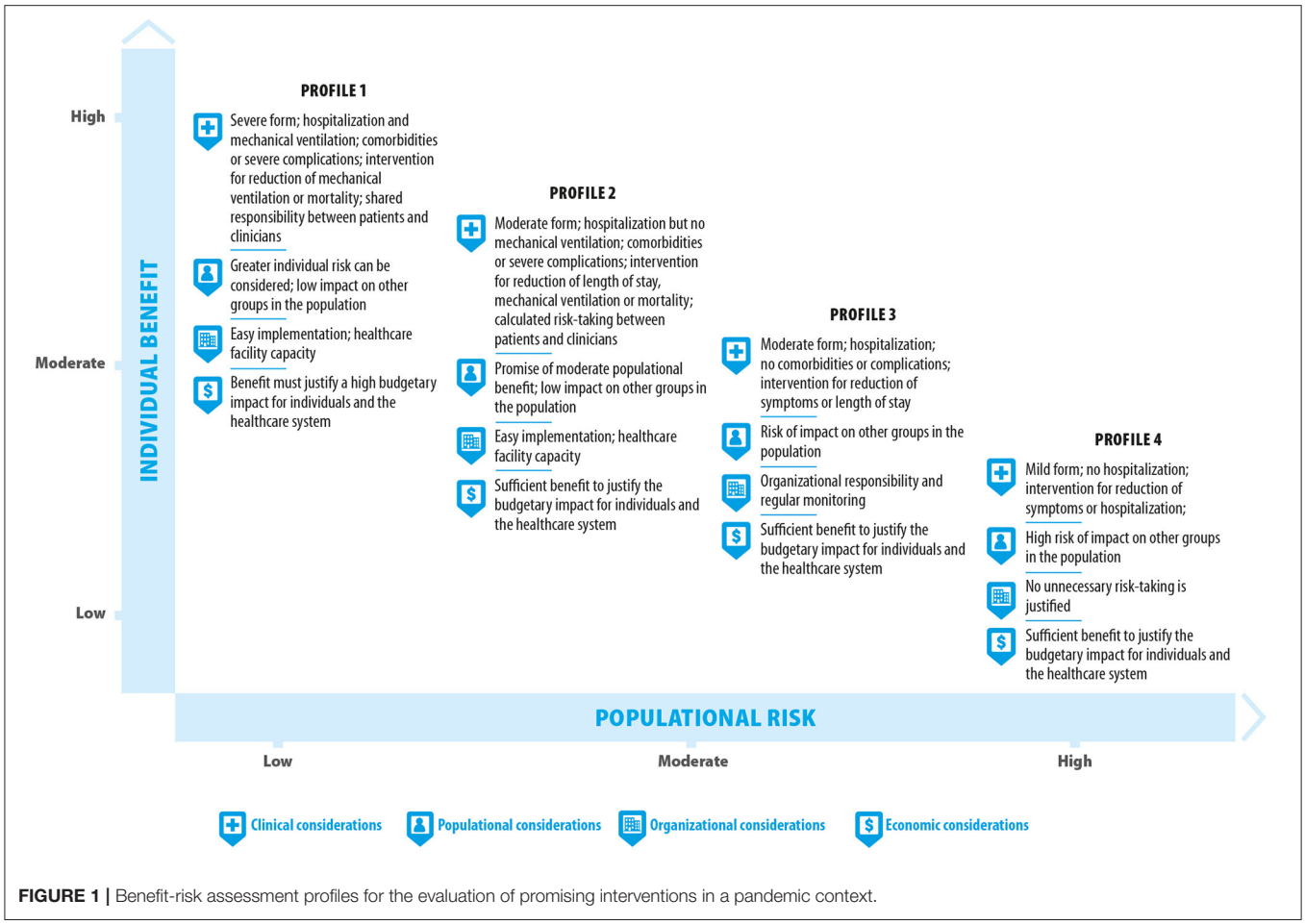

FIGURE 1 | Benefit-risk assessment profiles for the evaluation of promising interventions in a pandemic context.

the risks posed by the disease to the patients concerned or to the population. The decision-making process concerning access to the interventions under this scenario lies more with policy-making and organizational bodies. This profile could require organizational monitoring to revise the benefit-risk balance assessment in light of the course of the disease and patient care trajectories. To be acceptable, this access should show sufficient benefit relative to its budgetary impact on the healthcare system or on individuals.

Profile 4 Can Occur in a Situation Where Individual Benefit Is Expected to Be Low and Populational Risk High

This profile can occur when facing individuals with a mild form of the disease, not requiring hospitalization, and for whom the intervention considered is intended to reduce the symptoms of the disease or risk of hospitalization. Furthermore, access to the intervention in question is highly likely to create a shortage for other groups in the population. This profile engages populational responsibility on the part of policy-making bodies involved in the decision-making process. The benefit-risk assessment under this scenario should ensure that no unnecessary risks are incurred for the population, such as the risk of an intervention shortage or of unsuspected adverse effects. This access should demonstrate sufficient benefit relative to its economic impact on the healthcare system or on individuals.

Edwards defines such an approach as being adapted to the level of risk, and supports the notion that it is acceptable for the bodies and agencies responsible for evaluating promising interventions to require a lower level of evidence of benefit, in order to promote research and development of interventions for people with greater need in the context of the disease (40).

An approach adapted to the level of risk and the needs of individuals could permit differential value judgments based on their vulnerability and ensure respect of their right to try interventions, as was raised during the consultations.

DISCUSSION

Taking the identified ethical considerations into account suggests that the benefit-risk balance of promising interventions can vary according to the specific context of a pandemic and those most susceptible to its impact. This makes the evaluation and decision-making processes concerning promising interventions even more difficult when the evidence demonstrating their efficacy and/or safety is marked by uncertainty.

Overall, the present reflection demonstrates how decision-making concerning access to promising interventions in a pandemic context requires humility in the face of the available knowledge and the promotion of continued data collection to inform the social choices that will likely have to be made. It also suggests that the dissemination of scientific knowledge should preferably occur following its validation by peers. If deemed useful to occur prior to such validation, such dissemination should report its limitations in a clear and transparent manner. In light of this reflection, it appears that the benefit-risk balance assessment of promising interventions should take various factors into account, including:

- the severity of the disease;
- people's vulnerability to the disease;
- the uncertainty associated with the interventions' efficacy and safety;
- the populational impact of access to the interventions (e.g., risk of shortages);
- the individual and populational priorities regarding the interventions;
- the organizational capacity and feasibility of applying the decisions made; and
- the economic issues associated with access to the promising interventions.

The assessment model proposed by the McGill University Health Center for making decisions about access to care or interventions in a context of uncertainty or limited resources, or in rare situations, provides a new way of thinking about the issue of assessing the benefit-risk balance of promising interventions. The profiles proposed for conducting such assessments also appear to be supported by the risk-adapted approach described by Edwards for addressing the challenges of evaluating promising interventions in a pandemic context (40). In light of our reflection, it also seems necessary to adopt a framework involving several aspects to permit a thorough benefit-risk balance assessment and a global evaluation of promising interventions in a pandemic context. An assessment of the global value of the interventions using the model proposed by INESSS (39) would make it possible to consider all the aspects affected by the responses to a pandemic relating to the interventions being evaluated. The considerations and the approach to assessing the benefit-risk balance that emerge from this reflection can be applied to other contexts susceptible to fostering significant uncertainty surrounding the available scientific evidence, such as an epidemic setting.

While not limited to the COVID-19 pandemic, the literature review and the consultations that were carried out for the purposes of this reflection mainly paint a picture of the situation as experienced during this setting. However, the lived reality of the COVID-19 pandemic has shown the degree to which knowledge about the present subject was lacking. It seems that the lessons learned during previous pandemics were not sufficient to enable approaching the current one with confidence. Since the context in which each pandemic takes place might differ, the present discussion has limitations in terms of identifying the particular challenges that another pandemic might bring, particularly with respect to generating knowledge and assessing the benefit-risk balance of its specific promising interventions.

Regardless of the approach chosen to assess the benefit-risk balance of promising interventions, the primary responsibility for doing so still rests with the research teams and manufacturers conducting clinical trials. In this regard, clinical research conducted in a pandemic context should adhere to the standards and principles of responsible generation and dissemination of scientific knowledge, and:

- allow a clear demonstration of individual or populational benefits, taking account of the interventions' efficacy and effectiveness as well as associated uncertainty;
- report the uncertainty regarding the interventions' safety in a transparent manner;
- disseminate the research results in a timely manner;
- avoid being influenced by the urgency of the context and its accompanying pressures; and
- consider the special needs of people in vulnerable situations (e.g., pregnant women, the elderly, and people with chronic conditions and children).

Lastly, the benefit-risk balance assessment of promising interventions should seek to respect the principles of justice, equity, solidarity and transparency, which are essential for enabling the population to make free and informed decisions about their resulting supply.

CONCLUSION

The consultations conducted during this reflection demonstrated how decision-making in this regard should consider both the individual and populational priorities arising from the pandemic as much as possible. The dynamic between the various social actors brought together to discuss these issues allowed us to create a space of mutual understanding of the diverse perspectives presented. As the discussion moved forward, these perspectives became intertwined and allowed for the identification of ethical considerations which respect and integrate the views of all the participants. Although these results reflect the perspectives of a limited number of individuals, it was particularly rewarding to witness how the patient and citizen perspectives contributed to a shift in the thinking about the benefit-risk balance assessment of promising interventions.

AUTHOR CONTRIBUTIONS

CO contributed as the lead author to writing the manuscript and conducted the literature review and the consultations. IG and MG initially suggested carrying out this reflection and contributed to the group discussions. OD-P, LL, and M-PP contributed to the group discussions. SP contributed to the English version of the manuscript. All authors commented and approved the final manuscript.

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Patient Involvement in the Health Technology Assessment Process in Taiwan

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The COVID-19 pandemic initially had a smaller impact on Taiwan than on most other industrialized countries. However, an outbreak in late April 2021 led to a sharp surge in cases from mid-May 2021. Patient involvement in the health technology assessment (HTA) process, however, was not much affected by this; virtual meetings were implemented. This descriptive paper presents an overview of patient involvement in the HTA process in Taiwan via the National Health Insurance Administration (NHIA) online submission platform, participation in appraisal committees, education programs, and cooperation with patients' organizations, and outlines its progress and challenges. The National Health Insurance Act, amended in 2013, protects patients' rights and invites them to voice their opinions, which are then presented to the relevant authority. Based on this act, various mechanisms have been developed to involve patients, caregivers, and patient organizations in both the HTA and the reimbursement process. Prior to the Pharmaceutical Benefit and Reimbursement Scheme (PBRS) Joint Committee meeting, the NHIA built an online platform that allows patients to submit their opinions, which are then incorporated into the HTA reports. The results are also discussed with patient representatives, following which the related documents are published on the NHIA website. From May 2015 to December 2020, 30 patients' insights were published before the PBRS Joint Committee meetings. Of these, 19 (63%) were related to oncology cases. In Taiwan, approaches to fostering patient engagement include the use of a platform for patients' and patients groups' input, among others. Although patient engagement is important for understanding the needs of the target patient population, challenges in ensuring timely patient engagement and provision of relevant resources remain. In addition, further efforts are needed to implement and improve the visibility of patient input in the HTA process.

Keywords: patient involvement, health technology assessment, Taiwan, NHIA, Pharmaceutical Benefit and Reimbursement Scheme (PBRS)

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INTRODUCTION

In 1995, the single-payer National Health Insurance (NHI) program was established in Taiwan. This mandatory social health insurance is internationally known for its low premiums and co-payments. The NHI covers more than 99% of Taiwan's population (1). Taiwan began conducting health technology assessments (HTAs) in 2007 to support the National Health Insurance Administration's

(NHIA) reimbursement policies on new drugs (2). Adhering to medical ethics, the HTAs consider the health and well-being of all citizens as well as the cost-effectiveness of new medical technology within the financial framework of the NHI program. The HTA department operates under the supervision of the Center for Drug Evaluation (CDE) (2). In 2013, Taiwan implemented the second-generation National Health Insurance Act 2, with the HTA process, the composition of the Pharmaceutical Benefits and Reimbursement Scheme (PBRS) Committee, and transparency being written into the law. In addition, patient groups could now be invited to participate in PBRS Committee meetings (3).

The COVID-19 pandemic initially had a smaller impact on Taiwan than on most other industrialized countries (4, 5). However, an outbreak in late April 2021 led to a sharp surge in cases from mid-May 2021, mainly affecting the Greater Taipei area (6). Patient involvement in the HTA process, however, was not much affected by this; virtual meetings were implemented. In this paper, we focus on the development of patient involvement activities in Taiwan, while also comparing the current situation with that prior to the pandemic.

Patient Involvement in HTA Mechanism

In 2015, the NHIA announced the launch of a new page on its website specifically allowing patients, caregivers, and patient groups to submit their opinions about new drugs or medical devices. Thirty days before the scheduled PBRS Committee meeting, all input from the online platform was collected and summarized by the CDE/HTA division. The findings were then sent to the PBRS Committee meeting for consideration (7). The online platform was designed to include four main domains that would accept information regarding new treatment as well as personal details, the Declaration of Interest statement, and a statement from the patients regarding their perspectives on the experience (8). In 2016, the NHIA published a patient involvement guideline to assist the patient/caregiver/patient groups in expressing their opinions on the online platform more efficiently (7). Based on this guideline, only opinions on new technology that meet certain criteria are currently collected. For new drug applications, patient opinions are collected only if the product being discussed is related to treating the diseases included in the NHI's major illnesses/injuries list (7). On the online platform, patients, caregivers, and patient organizations can share seven kinds of information: the method of information gathering; experiences of living with the conditions/diseases; experiences of the traditional and new treatments; expectations regarding the new treatments; effects on caregivers with/without the new treatments; and other opinions (8). Patients' opinions are collected for at least 30 days before the application is listed on the agenda for the PBRS Joint Committee meeting (7, 9). The platform's questionnaire includes the following seven questions (8):

- How do you gather opinions? (personal experience, website, interview, focus group, survey, or others)
- How does your disease or condition affect your or your family's daily life?
- If you have not used this new treatment before, what is your current treatment? How effective is it? Have you encountered any adverse reactions or uncontrollable situations?
- If you have not used this new treatment before, what are your expectations from it? What kinds of conditions, adverse reactions, or quality of life do you hope for?
- If you have used this new medication before, how effective is it? Are there any adverse reactions? How does it affect your or your family's daily life?
- If you are a caregiver, please describe what kinds of conditions or adverse reactions on the part of the patient have affected your daily life.
- Is there anything else specifically related to your disease or treatment that you would like to mention?

The CDE/HTA team retrieves all opinions received via the platform, summarizes them, and then incorporates them into the HTA report. The report is published before the PBRS Joint Committee meeting, allowing stakeholders to learn about patients' experiences (7).

Although the webpage is established, the questions are simple and cannot adequately solicit information about patients' unmet medical needs. A participant may not know whether they need to answer all the questions or only a few. Thus, the current method is quite primitive, and changes must be made so that patients' voices can be heard clearly. Between 2019 and 2020, the CDE/HTA team set up more practical guidelines to help patients get their voices heard. It is hoped that these guidelines fulfill their purpose and motivate patients and patient groups alike.

Patients can participate in a PBRS Joint Committee meeting in two ways. First, two patient representatives are invited to attend the PBRS Joint Committee meeting (7, 9) and second, in a resubmission case, the NHIA can invite two disease-specific patient representatives to voice their opinions during the meeting (7, 9). In 2019, the NHIA revised the regulations governing the joint establishment of the NHI drug-dispensing items and fee schedule to allow two patient representatives to participate in the PBRS Joint Committee meeting routinely (9). The CDE subsequently developed a project to assist patient representatives in understanding more about the HTA process, diseases, and patient voices. The CDE/HTA team also holds a pre-meeting for patient representatives, beneficiary representatives (consumers) and case-related patient organizations, who have provided input on the platform to discuss patients' perspectives before the PBRS Joint Committee meeting. Moreover, in a resubmission case, the NHIA can invite patient organization representatives and listen to their opinions in the PBRS Joint Committee meeting for 10 min (7). Since 2016, the PBRS joint meeting has invited patient organization representatives to state their opinions.

Cooperation With Patients' Organization

In March, 2016, the Taiwan Alliance of Patients' Organization (TAPO) was established. Since then, more than 18 patient groups have joined the organization. All of which have an equal right to voice their opinions. The TAPO has also joined the International Alliance of Patients' Organization (IAPO) (8). The CDE, together with other related agencies and various patient groups, prepares

HTA reports and interacts with patients to ensure a better understanding of the HTA process and an effective, transparent government policy. From May 2015 to December 2020, 30 patient inputs were published before the PBRS Joint Committee meetings. Of these, 19 (63%) were related to oncology cases.

In some technology assessment projects, the CDE/HTA conducted interviews with patients regarding their experiences with trans-oral robotic surgery—four via telephone and one face-to-face. In this case, patient organizations assisted the CDE/HTA in finding appropriate patients to ensure that the final report included the views of those who had had experiences in open surgery, chemotherapy, or radiation therapy, so that these could be referenced by decision-makers.

In addition, there were some other projects related to the improvement of the patient involvement mechanism that involved a high degree of cooperation with patient organizations. In these projects, the CDE/HTA not only reviewed the experiences of patients from other countries, but also surveyed more than 10 patient organizations. It then set up an advisory committee with experts—which included patient representatives of the PBRS—and conducted six interviews with patient organizations. Through such cooperation, the CDE/HTA hoped that the patient involvement mechanism could become more structured and adaptable to local conditions.

Education of Patient Advocacy Groups

In 2016, the CDE/HTA established a patient involvement taskforce and initiated a series of educational programs for patients, caregivers, volunteers in hospitals, and patient organizations. Its main purpose was to introduce HTAs, the reimbursement process, and patient involvement mechanisms in Taiwanese populations. Since then, the CDE/HTA has conducted more than 15 training courses for patients, caregivers, hospital volunteers, and patient organizations focused on various disease types, like systemic lupus erythematosus, rheumatoid arthritis, cancer, psoriasis, development disability, and end-stage renal disease. These training courses were held across Taiwan, from Taipei to Kaohsiung, and even on the island of Penghu. More than 300 people took part. In addition, two international conferences for stakeholders were hosted in Taiwan, focusing on the questions "What is HTA?" and "How do we include patient voices in evidence?"

In 2018, the CDE/HTA developed instructions for patients, caregivers, and patient organizations using the online platform. In the following year, a review of patient involvement in HTA across various countries was prepared by decision-makers. This was meant to serve as a reference and provide information to patient organizations regarding patient involvement procedures in various countries.

In summary, **Table 1** shows the mapping of patient involvement in the health technology assessment process in Taiwan.

TABLE 1 | The mapping of patient involvement in the health technology assessment process in Taiwan.

Year	Key progress
1995	NHI program established
2007	Began conducting HTAs
2013	PBRS established, invite patient input
2015	Webpage/online platform established for patient input—4 kinds of information
2016	Patient involvement guideline on use of online platform
2016	Patient organizations invited to present at PBRS Joint Committee meeting
2018	Instructions on using online platform
2019	Two patient representatives on PBRS Joint Committee meeting
2020	Online platform established for patient input—extended to seven kinds of information for HTA report (released before PBRS meeting)
2020	Through the pre-meeting mechanism, discussion on patients' perspectives is conducted before the PBRS Joint Committee meetings, and feedback provided to them acts as input for the online platform
2020–2021	Patient opinions are put in HTA reports

DISCUSSION

In Taiwan, patients participating in HTA and the reimbursement decision-making process are fully supported by the NHIA. In this process, the CDE/HTA team plays a crucial role in supporting not only the NHIA, but also patients and patient organizations. Since 2015, patients have been able to engage in both processes in Taiwan through various mechanisms. Prior to the PBRS Joint Committee meetings, patients can report their experiences through the online platform; the CDE/HTA then summarizes these experiences and incorporates them into the HTA report. Discussions with the relevant stakeholders are also conducted before the meeting. Two patient representatives can participate in the meeting along with representatives of disease-specific patient organizations. After the PBRS meetings, the meeting documents and audio recordings are published on the NHIA website and made fully available to stakeholders and citizens. The deliberative process is thus more transparent and interdisciplinary.

Other HTA bodies, like the National Institute for Health and Care Excellence (NICE) in England (10), The Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada (11), and Scottish Medicines Consortium (SMC) in Scottish (12), have formal templates they use to collect patient evidence from patient organizations. The Pharmaceutical Benefits Advisory Committee (PBAC) in Australia has also constructed an online platform for consumers to provide their opinions (13). Taiwan's patient involvement process is similar to the PBAC's.

The importance of the patient perspective in HTA is increasingly appreciated.

However, some challenges remain. First, despite the multiple mechanisms that allow patients to engage with the HTA and the reimbursement process, the impact of such decision-making remains unclear. Few patients have chosen to share their experiences, especially those involving medical devices, via the online platform. This is likely because many patient organizations still are not aware of the platform, even though it is a major facilitator of patient involvement. Second, both the HTA agency (14) and patient organizations lack human

resources. The agenda for each PBRS Joint Committee meeting is published approximately seven days in advance (9), and patient representatives are expected to prepare patients' opinions on every single product in this duration. The scheduling leaves them with little time to get to know each case.

Because of this limitation, the CDE/HTA team references the guidelines The Health Technology Assessment international (HTAi) Interest Group for Patient and Citizen Involvement in HTA (PCIG) project has developed for patient organizations (15). Based on the NHIA's support, the questions on the platform are modified to cover different domains. Adopting the CDE/HTA team's suggestions has made the platform more comprehensive.

CONCLUSION

Patient involvement in the HTA process in Taiwan has shown that results can be delivered even when resources are significantly more limited than those in many Western countries. Taiwan's policy serves as a model for middle-income countries seeking to build patient involvement in the HTA framework. As HTA is interdisciplinary (16), it is important to obtain views on patients' involvement in HTA from people worldwide (15). Taiwan began involving patients in the HTA decision-making process in 2015. The practice is new, and the process still requires adjustments and modifications based on the experiences gained over time. Patient involvement is encouraged through the use of a patient input platform, group conversations, and other methods. Although patient participation is essential for understanding the needs of the target population, challenges concerning timely involvement and resources remain. Further efforts are needed to implement and enhance the visibility of patient input in the deliberative process.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

KC, LH, and CG contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

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Can We Afford to Exclude Patients Throughout Health Technology Assessment?

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Health technology assessment (HTA) is intended to determine the value of health technologies and, once a technology is recommended for funding, bridge clinical research and practice. Understanding the values and beliefs expressed by patients and health professionals can help guide this knowledge transfer and work toward managing the expectations of end users. We gathered patient and patient group leader experiences to gain insights into the roles that patients and patient advocacy groups are playing. We argue that through partnerships and co-creation between HTA professionals, researchers and patient advocates we can strengthen the HTA process and better align with service delivery where person-centered care and shared decision making are key elements. Patient experiences and knowledge are important to the democratization of evidence and the legitimacy of HTAs. Patient preference studies are used to balance benefits with potential harms of technologies, and patient-reported outcomes (PROs) can measure what matters to patients over time. A change in culture in HTA bodies is occurring and with further transformative thinking patients can be involved in every step of the HTA process. Patients have a right to be involved in HTAs, with patients' values central to HTA deliberations on a technology and where patients can provide valuable insights to inform HTA decision-making; and in ensuring that HTA methodologies evolve. By evaluating the implementation of HTA recommendations we can determine how HTA benefits patients and their communities. Our shared commitment can positively effect the common good and provide benefits to individual patients and their communities.

Keywords: patient involvement, patient engagement, health technology assessment, value, person-centered, patient-reported outcomes, patient preference studies

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INTRODUCTION

The COVID-19 pandemic has brought about many changes in our healthcare systems. Some of these can provide benefits for patients, such as widespread use of telemedicine and decentralized clinical trials (1). We have also seen many shortcomings regarding access to medicines and vaccines; and how we get more evidence and context to decision makers, clinicians and the public. Regulators, health technology assessment (HTA) bodies, payers and industry have learned the

value of aligning their processes, engaging with each other and creating more opportunities for international cooperation (2). Better alignment can convey information to decision makers in a timely fashion and assist them in dealing with uncertainty and change (2). The Medicines and Healthcare products Regulatory Agency (MHRA) as the UK regulator for market access has worked with patient advocates to develop and release its first patient involvement strategy (3), placing it in line with, for example, the European Medicines Agency (EMA) (4) and U.S. Food & Drugs Administration Agency (FDA) (5).

HTA is intended to bridge clinical research and clinical practice, and to determine the value of health technologies (6, 7). Understanding the values and beliefs expressed by patients and health professionals can help guide knowledge transfer from clinical trials to practice, and work toward matching the realities and expectations of end-users (8). Over recent years we have seen a progression from "should we involve patients" in HTAs (9), "can we afford to involve patients" (10), and a "call to action" (11) to the present situation with COVID-19 that indicates we cannot afford to leave patients out of HTAs (see **Table 1**). Partnership approaches are important to keep HTA aligned with the rest of the healthcare system where person-centered care and shared decision-making are key elements [e.g., (12)].

TABLE 1 | Key messages calling to strengthen patient involvement in health technology assessment.

Arguments for why patients should be involved in health technology assessments (9)
From a patients' rights perspective, patients have a right to participate in the planning and delivery of their health care, where HTA determines the health services, procedures and technologies available to them; building trust in the health system.
Value to patients is central to HTA deliberations and to healthcare systems. Centering on evidentiary contributions, patients can provide valuable insights to inform HTA decision-making.
From a methodological perspective, patients can help HTA methodologies to evolve.
Call to action for HTA agencies and all stakeholders to work together for meaningful patient involvement (11)
Goal 1: Working together with shared purpose.
Goal 2: A change in HTA culture, with integration of patient involvement.
Goal 3: Alignment with HTA agency goals, to improve health outcomes – and a positive impact on the diverse populations served.
Goal 4: Patient involvement at every step of the HTA process.
Goal 5: Transformative thinking that involves patient leaders, with use of a unifying language.
Can we afford to exclude patients throughout health technology assessments (present paper)
These steps are needed to ensure better use of healthcare spending:
1: Bring HTA in line with other parts of the healthcare system - we need to work as partners and co-create patient involvement in HTA.
2: Increase transparency and trust in technology development, regulation and funding informed by HTA - we all need to be honest about our different biases.
3: Activate an awareness and accountability system for how technologies are used in healthcare systems.

INVOLVING PATIENTS IN HTA

HTA addresses important questions that patients and clinicians share, including: does the technology work? If so, for whom, how well, and at what cost? Does it provide value for individual patients and the health system, does it fit within care pathways, and is it worth funding, largely on the basis of "cost" (7)? A health technology includes drugs, diagnostic tests, medical devices and healthcare procedures. HTA is defined on the basis of scientific rigor and evidence, with multi-stakeholder deliberations to appraise the evidence (13). The patient perspective is important in the democratization of evidence. Co-creation with patients can add to the legitimacy of the HTA process for the common good (14). Currently patient involvement is limited in its scope and barriers to their involvement include the lack of information to patients and public about HTA and the lack of policies (15–17), and the need for culture change (18–21). The "invited spaces" for patient participation have been set by HTA policy and practice and leave significant opportunities for broadening through mutual discussions (22). Public representatives have a place on the appraisal committees in a number of countries (17, 23, 24) and in some healthcare systems patients are payers in addition to being the focal point of what healthcare is about.

Abbreviations: App, mobile device application; CADTH, Canadian Agency for Drugs and Technology in Health; EMA, European Medicines Agency; EUPATI, European Patients' Academy on Therapeutic Innovation; FDA, U.S. Food and Drug Administration; G-BA, The Federal Joint Committee, Germany; HTAi, health technology assessment international; ICER, Institute for Clinical and Economic Review; KCE, Belgium Health Care Knowledge Center; MHRA, Medicines and Healthcare products Regulatory Agency, UK; NICE, The National Institute for Health and Care Excellence, England; PCIG, HTAi Patient and Citizen Involvement in HTA Interest Group; PRO, patient-reported outcome; SMC, Scottish Medicines Consortium.

As payers, patients are legitimate stakeholders within HTA. Their role as a payer can cause financial distress for patients (25). HTA is therefore an important methodology for health systems to make decisions on what services and technologies are funded and for universal health coverage (26).

Public awareness of healthcare has grown as a result of the COVID-19 pandemic, particularly in how infectious diseases spread, public health preventive actions, vaccine development, adverse effects of health technologies, regulatory processes, and the availability and distribution of protective clothing, medical interventions and vaccines. Healthcare systems have been stretched in many ways, including their capacities, access to equipment and technologies aggravated by arguments about how the disease is spread, use of face masks, and the science (27). These health system stresses have often meant that patient-centered healthcare has been side-lined, leaving people in critical conditions without their loved ones around them (28). Communication and support, including access to digital technologies, can be limited particularly for marginalized and vulnerable population groups (1).

In its June 2021 position statement, the International Network of Agencies for Health Technology Assessment (INAHTA) stated that "Patient involvement is recognized by INAHTA as an important and valuable element in the conduct of HTA" (29). In a plenary session of the HTAi 2021 Annual Meeting on "Patients at the Heart of Innovation" a call was made for person-centered HTA (30). There appears to be consensus that "we can do more,

and do better." HTA bodies calling for patient input often rely on patient groups to provide input that helps inform deliberations (24). Once received, patient input can be difficult to incorporate into the committee papers and formal assessment (20, 31, 32). Discussions are taking place to overcome at least some of these barriers (33). On occasion, the information provided fills a gap in knowledge or understanding of the appraisal committee (34, 35). And patients can make a difference as evidenced by an example of an assessment in sickle cell anemia for the Institute for Clinical and Economic Review (ICER). The sickle cell patient community highlighted "the appalling trade-off between choosing to manage intolerable pain from home or choosing to go to the emergency room, where many are met with racial prejudice, uninformed medical professionals, and a constant need to advocate for adequate pain management." Patients needed to meet a prior authorization requirement for opioid pain management, which hinders their access (https://icer.org/wp-content/uploads/2020/10/ICER_SCD_Response-to-Comments_031220.pdf). This raises the issue of need to optimize overall healthcare when providing a medicine or technology for treatment of a health condition.

ARE WE SEEING CHANGES IN APPROACH?

HTA professionals are looking to more "scientific" ways to provide patients' perspectives, as with syntheses of qualitative studies to provide patient evidence (36). Patient preference studies are now being extended beyond economic studies to build clinical trial evidence for an intervention or technology (37–40). Uptake in the USA has been slow (41, 42). In Europe however the Innovative Medicines Initiative (IMI) funded PREFER (https://www.imi-prefer.eu/about/) project involves patient groups to provide guidance for industry, regulatory authorities and HTA bodies on how and when to include patient preference studies on benefits and risks of medicines. The PREFER framework covers validated patient-reported outcome measures (PROMs), clinician-reported outcomes and observer-reported outcomes within a disease setting. These are used to weight the clinical trial evidence. How preference studies relate to patient input into HTA processes and actively involving patient advocates and patient advocacy groups is less clear. The IMI H2O Health Outcomes Observatory project (https://health-outcomes-observatory.eu/) involves patient groups and is creating a data governance and infrastructure model to collect PROMs and incorporate them into healthcare decision making at an individual and population level. Patients have ultimate control of their health data in this project. Qualitative studies that are used to inform patient preference studies are the type of studies that would make PROMs more meaningful and could help individual patients and patient groups better monitor their health conditions and the effects of treatments (43–45). As examples, Janssens et al. (45) showed that for people with multiple myeloma life extension is not the only thing they want from treatment. They want to retain the ability to carry out their daily activities and to maintain independence and mobility. Permanent and severe side-effects and symptoms are of concern to them. ICER noted that the US Food and Drug Administration (FDA) approvals covering drugs for relapsing remitting multiple sclerosis (MS) were based on reductions in the number of relapses. Patients told ICER that accumulating longer-term functional disabilities were the most important outcome for them (ICER HTAi 2021 presentation—personal communication). In an oral presentation at the same meeting, patient advocates highlighted the importance of upper body function and independent living for people with progressive MS who were in wheelchairs (https://youtu.be/hB_eII-b0P8). PROMs are important in capturing "what matters" to patients (46). Patient groups are already forming partnerships to develop apps to personally collect data to monitor and report on their condition, its evolution and the effects of interventions. An example is "Patient Voice – myGUT" in collaboration with Microsoft (personal communication).

Patient-reported data not only has the capacity to empower patients in managing their own health condition but also contributes to broader knowledge that can inform healthcare more generally, including HTAs (47, 48). Patients have felt that they are peripheral to the HTA process and that their involvement takes place too late in the process to make any real difference. Patient involvement is needed early and through all stages of the HTA process from topic selection, scoping, examining evidence, appraisal committee deliberation to determine value, and in formulating recommendations for funding or subsidy (11, 29). An early experience from one co-author, as a "patient expert" at an HTA appraisal, highlights this:

> *"I was led into a room with a very large table. Everyone had their heads down and were very intent on what was in front of them. When prompted, I started talking but I was very quickly interrupted and told they had read my "testimonial statement" in the committee papers. They did not need anything more from me... I went there to provide a voice to the voiceless, but left feeling that I had been gagged…"* Patient advocate

This example and others from the literature (11, 23, 32, 49) highlight that we need to address what patients and patient groups are being asked to do in HTA and why.

HOW CAN WE FACILITATE CHANGE?

We advocate that collectively, and at all stages of the HTA process, we can integrate the voices of patients, their advocates and support groups. We propose working together to democratize HTA processes, from governance to making recommendations on specific interventions. We see this as a right (9). Frank, comprehensive and respectful conversations are needed with patient advocates and patient advocacy groups about where and how they can provide fruitful, positive and meaningful contributions, and what impacts and benefits these can achieve.

Currently, patient advocates and patient groups may not have a clear understanding of the earlier stages in the development of the technology and in the HTA process, or know if patients or patient groups were involved. They also need clarity about

what treatments are already available, at what cost, with what treatment effectiveness, burden and side-effects, and for which sub-groups of patients. Background and landscape analyses can help patients offer more complete understanding and perspectives on the value of a particular technology as they explore and explain the trade-offs that patients must face. Yet scientific and medical jargon can deter patients from joining conversations. Health literacy principles apply and facilitate learning and mutual understanding (22, 50). Patient and public participation should have a direct effect on policy and decisions with inclusion of people's values, ideas and sentiments such that all participants can "live with the result" (22).

Transparency and trust in technology development, regulation and funding informed by HTA can be increased if we all are transparent about our different perspectives, limitations and biases. We also need open discussion on the conflicts of interest of each person involved. For example, HTA appraisal committees may be uncomfortable hearing about individual patient experiences and unmet needs (49), or they may not see the relevance of patients being present.

> *"Patients/patient group representatives are often not really listened to when they speak. The expectation is that they just want the new [better] technology, and they are in league with industry anyway."* Patient advocate
>
> Yet, *"patient advocates tend to change the environment and tenor of the discussion. This gives people on all sides the space to say things they may not normally feel comfortable saying—when "we let them"."* Patient advocate

An example from ICER shows where a new treatment for sight loss (blindness) failed to achieve traditional measures of cost-effectiveness. Patients and their families conveyed how extensive the benefits of better sight (even partial) are for the entire family through improvements in school, work, and social functioning. ICER developed an alternative economic model incorporating these benefits that was accepted as a reasonable long-term value (HTAi 2021 presentation, personal communication). The value for patient communities needs to be clear. It is also important to understand at the start what the place of the technology is: is it a "breakthrough" technology, another me too, an older product revitalized? This can have an impact on the amount of time patient advocacy groups spend on preparing patient input.

> *"On an HTA appraisal committee I was asked why I was not supporting approval of a cheaper, less effective drug. I was able to state very clearly because if approved it would be used and would make it more difficult for patients to access treatments that were much more likely to be effective, and so prolong their discomfort and suffering."* Patient advocate
>
> *"We need to challenge patient groups to take more responsibility for better outcomes for their patients by insisting that we get better, not just more, treatments. And that they add value to patients' lives without causing them to go bankrupt."* Patient advocate
>
> *"We should show how we represent a group of patients, not just our own experience. Part of the responsibility of an HTA patient advocate is to give a spectrum of issues and experiences. This approach helps build our credibility, and necessitates our authority as peers with specific expertise on the perspectives of service users."* Patient advocate

In recent years patient advocates and their organizations have become better informed, educated and trained to concentrate on their patients' experiences and knowledge so to effectively contribute to regulatory and HTA decision-making [e.g., (37, 51–53)]. They are also involved in clinical trial design (54, 55). Now we need to co-create and democratize the evidence (56). Patient advocates and patient advocacy groups need to have access to comprehensive, informative data on the technology they are being asked to comment on, which often does not happen (22). The justification of not sharing the data on a technology is that manufacturers need to protect confidential and proprietary information, and laws on "advertising prescription technologies" to the public that interrupt adequate flows of information (57). A non-disclosure agreement (NDA) is already used by the HTA body for the other members of the committee and can also be used for patients. Clinical trial reports may be behind journal paywalls or not accessible to the public; similarly comparative data, longer-term and real-world data. Some HTAs have tried to resolve these limitations. The Scottish Medicines Consortium "Summary of Information for Patients" (SIP) is a simple summary of clinical trial data for patient groups to be provided by industry as part of its product submission that is being used to develop similar processes in other countries (58). While promising, the authors of this paper are concerned that industry may essentially control what patient advocacy groups know about the new technologies.

> *"We are "selling" something to patients without giving them the background information and evidence-base that they need to be able to make rational choices/judgements."* Patient Advocacy Group

Germany's Federal Joint Committee (G-BA) ensures that its patient advocates receive full information (59), HTAi 2019 PCIG workshop—personal communication], demonstrating that "political commitment" can overcome these information barriers (22). "Partnership synergy" is the ability to work together by combining resources in order to produce an output that cannot otherwise be achieved by single agents (22). This is for "the common good" and fosters democratic discussions where the quality of the dialogue is dependent on the quality of the information provided, together with a trusting relationship between participants (22).

Finally, optimizing and measuring how technologies are used would ensure the most effective use of technologies, and how healthcare systems could derive the greatest benefit from them. HTAs often ask medical professionals, researchers and public members of an appraisal committee to judge what patients think about a new treatment and its potential benefits and harms, ironically while restricting patient advocate and patient advocacy group input. Information directly from the source is always more reliable.

TABLE 2 | Patient advocate and patient advocacy group concerns with examples of what is being done related to HTA bodies.

Past concerns	What is happening	What could happen
Public awareness and understanding		
Public awareness about technology development, regulation and funding including through HTAs.	COVID-19 has greatly increased public awareness about the development and regulation of medical technologies. Less so for HTA (61). CADTH Patient and Community Advisory Committee—to help explain how policies and activities impact patients, families, communities (62). https://www.cadth.ca/patient-and-community-engagement.	Continue to work on increasing public awareness—explaining processes and who is involved. Harmonize the language used. Patients can understand information when clear and visual—and sufficient data available (e.g., https://eczematherapies.com/patients/). More patient involvement and engagement at governance level. As with the HTAi Patient and Citizen Involvement Interest Group (PCIG) project: "Patient participation at the organizational level in HTA". https://htai.org/interest-groups/pcig/projects/current-projects/.
Guidance and transparent policies on prioritization of technologies, and in developing new technologies—so that it is not largely dictated by what industry has "to offer"; or what governments "want to buy."	National medicines policies (63). Prioritization project in South Korea (64).	Open access to information looking at global market access to health technologies for different health conditions. ICER is to publish their updated process and experience with patient advocates and patient groups (personal correspondence with their Vice President, Patient Engagement).
Diversity and health equity, account for vulnerabilities.	CADTH Patient and Citizen Advisory Committee (62).	
Need for emphasis on "value to patients," their "unmet needs" and major concerns; attention to and consideration of care bundles and not just the technologies in isolation.	ICHOM (https://www.ichom.org/), H20 (https://health-outcomes-observatory.eu/). All CAN (https://www.all-can.org/efficiency-hub/) ICER (e.g., lupus nephritis): https://icer.org/wp-content/uploads/2020/11/ICER_Lupus-Nephritis_Policy-Recommendations_041621.pdf	Through wide use of carefully selected and developed patient-reported outcomes. In Spain, consensus expert recommendations representing all stakeholders in AMPHOS (https://sedisa.net/wp-content/uploads/2019/12/informe_de_AMPHOS-07-2.pdf) and other initiatives. In specific pathologies, measure quality of care taking into account different dimensions: CUE (65) in inflammatory bowel disease (IBD), not publicly funded.
Patient input		
Requests for patient input as comments or submissions, often made too late to contribute effectively to the HTA process.	KCE—input into assessment (66). UK—in scoping for an HTA (24). Guidance on how to involve patients in HTA in the Spanish Network RedETS are presented in a flowchart. Patient organizations or expert patients can participate in protocol development, outcomes' identification, assessment process, and report review (67).	Establish well-trained and selected "patient involvement reference group" at HTA management level to work collaboratively with HTA professionals and the patient and public involvement team (where it exists). Medical professionals included, particularly those experienced in shared decision making and person-centered health care. Work with researchers and HTA professionals to improve methodologies for patient/patient group input at all stages of the HTA process.
Information for patient advocacy groups to develop patient input		
Keep patient advocacy groups informed, e.g., if a technology is too expensive to recommend for funding; and its likely place in a care plan i.e., if there are a number of similar technologies already.	Patient groups may only be presented with "part of the story," which can create mistrust. When invited to participate, data provided is full of acronyms and tables, with no guidance on its use. ICER Lupus nephritis summary recommendations (as above).	Working with the concept of patient and clinician driven "hope" and its place in the value assessment and use of health technologies.
Patient advocates and patient advocacy groups may find it difficult to develop the skill set and support for their work in HTAs. The training sessions that are available may be general or limited to particular aspects.	Training programs run for example by the FDA in the USA, EUPATI and WECAN in the European Union, INVOLVE in UK. The training is theoretical—still a need for manuals and other support materials (checklists, examples) to guide and assist people.	Enlist "patient coordinators" and "patient partners" (60) to provide peer support; build on skills including critical appraisal of clinical trials and other data; preparation and analysis of own data. Build "patient involvement reference group." Publications from patient advocacy groups.

(Continued)

TABLE 2 | Continued

Past concerns	What is happening	What could happen
Patient advocates and patient groups may not have ready access to clinical trial and economic data for the new technology.	Lay summaries provided (58). The new drug evaluation system in Spain (REvalMed) (68) sends economic comparisons, efficacy and safety data to the patient associations consulted. This is making it easier for us to provide our feedback.	Access to full summaries of clinical trial and economic data; and how the data analyzed in an assessment, and on what basis.
Incorporating patient input into HTAs		
Difficulties in incorporating patient input into appraisal committee papers.	We built as a "pilot" a simple and inexpensive multi-criteria decision analysis (MCDA) framework so that patient associations could analyse and compare the value of treatments (69).	Encourage research on methodologies that would strengthen patient input and bring it into the HTA process. Support sound methodologies for patient involvement and data collection. ICER https://icer.org/work-with-icer/patients/.
We need new methods for collecting data to inform patient input into HTAs. Patient advocates and patient advocacy groups may not be funded to gather data. If they receive any funding, could create conflicts of interest.	Use of PROs and digital technologies such as apps to collect data on a disease and its treatment. Quality of life measures used as numerical tools to estimate utility and population data rather than giving a true measure of what the patient is experiencing; and without including the career.	IMI H2O open data project—important that all stakeholders have access to the same data to validate or refute the information. Projects like H20 offer this advantage. (https://health-outcomes-observatory.eu/). NICE review of methodologies (https://indepth.nice.org.uk/methods-review/index.html).
Not all patient advocates are active members of disease-specific patient advocacy groups; and not all patient support groups or charities advocate on behalf of patients as individuals. This can be a serious problem.	Some countries such as Australia accept input from individual patients, careers etc. as well as from patient groups*. The EMA does an assessment of the person by verifying their capacity and evaluating the evidence they provide to lend credibility to their discourse.	
Follow up of funding decisions		
Follow up of how technologies are utilized in clinical practice, if their use is directed to patients who can benefit from them, if associated with added expenses; and how the care pathway enables optimal use. We want good decisions about access to and affordability of technologies.	Valtermed** in Spain for higher-priced drugs, an access and tracking mechanism to monitor the outcomes the drugs achieve (and set pricing and payment methodology, pay-for-outcome). Registries in Italy and clinical audits (70).	A decalogue of "Quality of Care" indicators from the patient's point of view, the IQCARO project (71). Registries in Italy also used with Covid-19 (personal communication).

**Available at: https://www1.health.gov.au/internet/hta/publishing.nsf/Content/consumers.*

***Rosa F Valtermed: la conexión y el registro de resultados clínicos ya es posible. (2019). Available online from: https://www.diariofarma.com/2019/07/22/valtermed-la-conexion-y-el-registro-de-resultados-clinicos-ya-es-posible.*

> *"The regulatory and approval systems focus on efficacy of the product, not effectiveness of its use in or with people. The public is not told about this difference and often assumes that the product is effective when this has not been evaluated..."* Patient advocate (US)

STEPS TO LEAD FORWARD

Working together in partnership is transformative and can help HTA bodies to understand how to invest in active, meaningful patient engagement (22, 60). Patient participation can help to ensure that HTA agencies are aligned with the end-users [(11), https://icer.org/wp-content/uploads/2020/11/ICER_Lupus-Nephritis_Policy-Recommendations_041621.pdf].

A system to monitor and provide feed-back on how technologies are being utilized within the healthcare system, and for whom, could complete the loop for evaluating the implementation of HTA recommendations. This can create a "learning HTA and healthcare environment" that measures outcomes to inform them and builds on value over time [US Agency for Health care Research and Quality (AHRQ) https://www.ahrq.gov/learning-health-systems/index.html]. In the longer-term we would all learn to trust and benefit from availability of the most appropriate and effective technologies.

In **Table 2** we have summarized our concerns together with examples of what is being done related to HTA bodies.

CONCLUSIONS

Patient advocates and patient advocacy group leaders share common interests and goals with HTA bodies regarding good decisions about access to, and affordability of health technologies. Greater benefit and effectiveness can be generated by integrating patient advocates and patient advocacy groups into HTAs, rather than treating them as separate from decision-making bodies. Good progress is being made by the HTA community. It is now time to develop consistent emerging practices globally, and to measure the results of HTA recommendations in ways that benefit the health and welfare of patients and their communities. We call on HTA leadership to work with us to build pro-active, iterative participatory methods that engage and integrate patient input into the technology development and HTA continuum.

Our shared commitment can positively affect the common good as well as provide benefits to individual patients and their communities.

DEFINITION OF TERMS AS USED IN THIS PAPER

Co-creation, co-design and co-production: Terms used interchangeably in this document to describe equal status partnerships between patient leaders and HTA bodies.

Democratization of evidence: Developing a better understanding and use of evidence.

Legitimacy: Where "democratic legitimacy" incorporates a broader view of evidence to inform efficacy, utility, and effectiveness; through inclusion and equity of allocation of resources.

"Scientific legitimacy" involves the application of scientific rigor and objectivity, leading to scientific policy goals rather than population goals.

Healthcare technologies: Services, diagnostics, medicines, medical devices and digital devices for use in health care.

Patient input: Includes patient advocates/patient group representatives on a committee, patient experts presenting at a committee meeting, and patient and patient group submissions for an HTA. This can also include caregivers.

Patient leaders: Patient advocates and patient advocacy groups who are active in building and strengthening patient involvement in HTAs. We describe patient leaders as people who can envision where changes to bring about solutions can take place, and work with others to enable change. McNally (72) used the term "patient leadership" to describe an investment in patient and career leaders working collaboratively in co-creation, co-design and co-production projects.

Patient and public involvement and engagement: A purpose of patient involvement in HTA is to improve the legitimacy of decision making; and is instrumental in producing better quality decisions that reflect patient and public preferences and values, through transparent, accountable, legitimate processes.

Person-centered HTA: The involvement of patients throughout the HTA process to build on patient input that has taken place in earlier stages of technology development, such as in basic research, patient preference studies, clinical trials and in being part of regulatory processes. This term was first publicly used at the plenary session "Patients at the heart of innovation" during the HTAi 2021 Annual Meeting (30).

Service end users: People who use the healthcare system for prevention or for treatment. Most often known as "patients."

Stakeholder: Any group or individual who can affect or is affected.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

JW, DCh, DCo, DH, RS, and ZP-W contributed to the discussions and preparation of this manuscript. All authors contributed to the article and approved the submitted version.

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Where National Medicines Policies Have Taken Us With Patient Involvement and Health Technology Assessment in Africa

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The Covid-19 pandemic has highlighted global knowledge about, but lack of equitable access to, life-changing medicines, and other innovative medical products by populations in African low and middle income countries. The World Health Organization (WHO) and other international non-profit foundations and organizations are constantly striving to address inequity. In the 1970s, WHO initiated a regularly updated essential medicines list, together with the concept of national medicines policies (NMPs) to ensure access and availability, affordability, rational, and effective use of medicines which are considered essential in addressing predominant population health issues and disease burden. We studied the NMPs of Ghana, South Africa, Uganda and Zimbabwe to highlight some of the important issues that these countries experience in the safe and effective use of medical products. Thailand is an example of how health technology assessment (HTA) can provide a country with an internationally supported, clearly defined and transparent process to broaden access to medicines and services. These medical services can add considerable value in accordance with local values and priorities. Involvement of civil society adds democratic legitimacy to such processes. Community health workers and patient advocacy groups are important in raising awareness and knowledge of safety issues and the effective use of quality medicines. They can apply pressure for increased funding to improve access to healthcare. Medicines and services that contribute to supported self-care are of benefit in any setting. Joint efforts across African countries such as with the African Medicines Agency are important in addressing some of the major health issues.

Keywords: patient involvement, civil society, health technology assessment, national medicines policies, regulation, globalization, low and middle-income countries

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WORKING TO ACHIEVE ACCESS TO HIGH QUALITY MEDICINES AND RATIONAL PRESCRIBING IN LOW AND MIDDLE INCOME COUNTRIES

In April 2020, >3 months into the Covid-19 pandemic, the World Health Organization (WHO) together with a number of nations launched a cross-discipline partnership to enable resource and knowledge-sharing. The Access to COVID-19 Tools Accelerator included a COVID-19 Vaccine Global Access (COVAX) pillar. Its aim was to rapidly scale up the delivery of vaccines to address

high-risk target groups through a scheme of fair distribution (Accelerator) (1). Over time, people without access to resources such as strong health systems, health workers, medicines, and vaccines have become the majority of those who develop Covid-19 infections and die. One publication reported that by late June 2021, 46% of people in high income countries had received at least one dose of Covid-19 vaccine compared with 20% in middle income countries and only 0.9% in low income countries (2). Equitable vaccine distribution was clearly not happening. Broadened vaccine development and approval; scaling up of manufacturing; streamlining shipment, storage, and distribution; and building vaccine confidence were called for. Production and the supply chain was recognized as a barrier to access by high-risk populations and to global vaccination (3).

The 1995 Trade Related Aspects of Intellectual Property Rights (TRIPS) Agreement was set up to provide minimum protection standards for intellectual property, which included pharmaceutical products and vaccines (4). South Africa and India submitted a proposal to the World Trade Organization (WTO), in October 2020, to allow licensing of Covid-19 health products and technologies under the TRIPS agreement (2). They and other countries would then be able to produce Covid-19 medical goods locally and effectively import or export them. India, Egypt, and Thailand were already under license to manufacture viral vector or mRNA-based Covid-19 vaccines. With TRIPS any compulsory licensing arrangements are restricted to domestic purposes only. In order to broaden availability of vaccines, WHO set up an mRNA technology transfer hub in April 2021 to provide the support needed for manufacturers in low and middle income countries (LMICs), and South Africa was selected as the first hub (2).

India has over the years aimed for "abundant availability on a continuous basis, at reasonable prices, of essential, lifesaving and prophylactic medicines of good quality" through local production, generic products, and by managing its tariffs and taxes (5). Standards were benchmarked and harmonized with international standards and practices to ensure high-quality, safe and efficacious pharmaceuticals and to enable growth of an export industry.

Inequities in access to Covid-19 vaccines are simply the latest manifestation of a longstanding problem for Africa and other LMICs. As the prices of medicines and vaccines continue to rise worldwide (6), many LMIC populations are unable to access essential products and are dependent on donations which are often inferior in quality and effectiveness. The WHO has been a key player in more equitable, affordable accessibility to health technologies. Its activities include developing an essential medicines list to prioritize access to and availability of pharmaceutical products, and their rational use (7). The WHO Model List of Essential Medicines (EML) is a list of the medications considered to be most effective and safe in meeting the most important needs in a health system (7). The first list was published by WHO in 1977, and the list is updated every 2 years. Core items are judged to provide the most cost-effective options that require few additional healthcare resources. Other items require infrastructure such as trained healthcare providers, diagnostic equipment, or have a lower cost–benefit ratio. A separate list was created for children in 2007 (6, 7).

Regulating the products entering a country, efficient procurement and ensuring safe and effective distribution are key elements that may be inadequate because of limited funding and lack of a skilled workforce. In response to defined needs, WHO developed and promoted the concept of national medicines policies (NMPs) (8). Of the many WHO programs that support African and other LMICs in their ability to provide medicines to their populations, supporting development of NMPs is one such program (8, 9).

In this perspective we describe how LMICs have used their NMPs to provide essential medicines, improve the safety and quality of medicines, extend their EMLs, and apply rational use of medicines. The introduction of health technology assessment (HTA) processes and the African Medicines Agency are seen as opportunities to broaden discussions on the value of medicines and other technologies and for more unified action to ensure the availability of quality medicines for a wide range of diseases as countries commit to achieving universal health coverage (UHC) by 2030 (10, 11). Each country has its own healthcare challenges that may relate for example to the national political situation, economics and existing legislation. In LMICs access to medicines can be a major issue for the leading politicians and is dependent on the political values of the government, the level of spending on medicines and economic development, and commitment to providing their population with medicines (12).

NATIONAL MEDICINES POLICIES (NMPS) AND THEIR ROLE IN PROMOTING ACCESS TO AFFORDABLE MEDICINES AND RATIONAL PRESCRIBING

NMPs and Their Goals

Medicines are an important part of healthcare, and the cost of medicines is a key driver of cost of healthcare in African countries. The concept of a NMP was first introduced by the WHO at the 28th World Health Assembly in 1975. The NMP is presented and printed as an official government statement with a framework setting goals and guidance for action (8). The understanding is that for LMICs priority is given to a limited number of carefully selected medicines based on the overall needs of the population. The use of these medicines is supported by agreed clinical guidelines, better supply and procurement, more rational prescribing, and lower costs (9).

Focus on NMPs for Ghana, South Africa, Uganda, Zimbabwe

We studied NMPs from Ghana (2017), South Africa (1995), Uganda (2015), and Zimbabwe (2011) to gain an understanding of their policies (**Tables 1**, **2**) and the issues they address (13–16).

Uganda (15) sees the objective of its NMP as "contributing to the attainment of a good standard of health by the population, to meet the currently recognized needs of the majority of the population." The Zimbabwe NMP (16) sets out to "improve, within available resources, the health of the majority of the

TABLE 1 | National Medicines Policies (NMPs) studied, together with their stated objectives.

Ghana 2017 (13)
To bridge equity gaps in geographic access to health services, ensure sustainable funding for healthcare delivery, improve efficiency in governance and management, strengthen prevention and control of communicable and non-communicable diseases, and improve quality of health services including mental health.
South Africa 1995 (14)
To ensure the safety, efficacy and quality of drugs; good dispensing and prescribing practices; rational use of drugs by prescribers, dispensers and patients through provision of necessary training, education and information; and to promote the concept of individual responsibility for health, preventive care and informed decision making.
Uganda 2015 (15)
To ensure availability and access to affordable drugs to meet the currently recognized needs of the majority of the population.
To provide objective, relevant, and practical information to health workers, patients and the general public.
Zimbabwe 2011 (16)
To improve (within the available resources) the health of the majority of the population by treating, curing, reducing or preventing diseases and disorders of health. Equitable availability, accessibility, and affordability of essential medicines, especially to the vulnerable segments of the population, with a focus on priority health problems and, rational use of medicines by health professionals and consumers.

population by treating, curing, reducing or preventing diseases and disorders of health" (Zimbabwe). Some NMPs focus on a country's priority health problems and the rational use of medicines by both health professionals and consumers (Uganda, Zimbabwe). Good prescribing and dispensing practices; rational use of drugs by prescribers, dispensers, and patients, by providing necessary training, education, and information; and promotion of the concept of individual responsibility for health, preventive care, and informed decision-making (South Africa) are all pertinent elements.

How NMPs Promote Access to Medicines and Rational Prescribing

The NMPs place an emphasis on developing expertise and human resources in all medicine-handling activities to support successful implementation of the NMP policies (Ghana, South Africa). Training of health workers, including in under-served regions, with sufficient numbers of pharmacy personnel (pharmacists, pharmacy technicians, and dispensing assistants) are specified (Uganda, Zimbabwe). Rational use of medicines is described by WHO as where "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community" (17).

Good-Quality, Safe, and Effective Medications

A key component of a NMP is to ensure the safety, efficacy, and quality of medicines, where an emphasis is placed on

TABLE 2 | Issues addressed by national medicines policies in the selected African countries.

The main aim of a National Medicines Policy in the selected African countries is to make available and accessible medicines with the required clinical effectiveness, safety, and quality for evidence based use, and that those provided are cost-effective in their therapeutic group and appropriate to that country
- To have a healthy and productive population that can reproduce safely
Selection of essential medicines and health technologies
- Use of an essential medicines list held by government
- To meet the currently recognized needs of the majority of the population
- Standard Treatment Guidelines (STG) as part of the Essential Medicines List
- Reference guidance
Economic objectives
- National health policy in alignment with national development
- Lower the cost of drugs (in private and public sectors) through local production
- Support development of local pharmaceutical industry
- Cooperation with regional and international agencies
Pharmaceutical legislation and regulations
- Registration of drugs and supplies
- Registration of practitioners
- Licensing of premises; inspections
- Appropriate legislation and regulation on medicines and medical supplies
- Regulatory standards and specifications
- Quality assurance and control
- Post-marketing surveillance, monitoring of adverse medicine reactions (Zimbabwe)
- Advertising, provision of information
- Tariffs and taxes
Governance
- Good governance, transparency, and accountability of the pharmaceutical sector
- Risk management
- Organization, management, co-ordination, evaluation of the National Medicines Policy
Quality assurance
- Good drug quality control
- Monitor the quality of medical products in circulation and quality defects
Drug funding
- Allocation of funds to the public sector so that required essential drugs are continuously available
Drug pricing
- Rationalization of pricing structure
- Use of generic drugs
Appropriate selection of medicines
To provide quality, safety, efficacy and stable dosage forms. Improve the understanding by health workers, patients and the public on essential drugs (Uganda)
Local manufacture of drugs
Incentivize local production of (essential) medicines
Ensure information on current needs for medicines and the supply situation
- Ensure uninterrupted supply of medicines
- Avoid wastage and drug expiry caused by over–estimation of requirements, and procurement of low–quality or short shelf–life drugs

(Continued)

TABLE 2 | Continued

Drug supply and availability of medicines through procurement, distribution, storage
- Procurement (including donations)—capacity, skills, and experience at all levels of the health system
- Storage and inventory control
- Distribution—quality maintained up to the point of use. Develop procurement so that a system is established
- Optimize utilization of available funding
- Develop trust of the public, donors and all other interested parties in the credibility and validity of the medical supplies management system
- Avoid drug leakages, absence of proper stock management information, and poor storage conditions
Rational use of drugs
- Promote rational prescribing, dispensing and use of medicines, by all health personnel
- Ensure that health workers and the general public have access to accurate, up-to-date, unbiased, relevant information on medicines and their use
- Support informed and appropriate use of medicines by the community
- Adhere to ethical criteria for medicines advertising and promotion
- Improve understanding on the place of medicines in a person's treatment
- Ethical procedures in handling medicines, including over-the-counter
- Practical and relevant information on the correct use and storage of medicines
Use of medicines, information
- Only obtain medical supplies from suppliers who have acceptable quality standards and procedures
- Promptly address and resolve the quality concerns of health professionals and consumers
- Patient safety
Disposal of expired or otherwise unwanted drugs and medical supplies
- Safely dispose of expired and unwanted medicines and related health technologies
- Reduce loss, wastage, and hazards from poor practices throughout the supply chain
Human resources development
- Training, recruitment, retention, and development of well-trained health workers at all levels of the health system
- Set and maintain high standards and efficiency in medicine management and handling
- Improve local pharmaceutical technical capacity by training staff in production, quality assurance and Good Manufacturing Practice
Research and development
- Operational and Technical Research and development
- On the National Drug Policy
Global trade
- Export locally manufactured medicines and vaccines
Technical cooperation with other countries and international agencies
Health technology assessments
- Collaborate with other HTA groups regionally and globally, to contextualize existing knowledge when available
- Implementation
- Transferability
- Transparency
Emerging diseases and pharmaceuticals
- Collaborate with the relevant international organizations to mobilize resources
- Support and fund the research, development and local manufacture of needed products

procurement of generic medicines and the promotion of their use as a means of reducing costs (South Africa, Uganda, Zimbabwe). The Ministry of Health in Ghana with support from development partners centrally procured a number of products in an effort to improve quality. Supply through donations and development partners is a recognized source of medicines in Africa (Ghana), for example in the treatment of tuberculosis, HIV/AIDS, malaria, and in providing Ebola vaccines.

Good governance, management, transparency and accountability, and risk management are important in the procurement of medicines (Ghana, Zimbabwe). For medicines to be continually available and of good quality, a number of factors need to come together including supply to the country, procurement in the public sector, distribution, storage, and inventory control. Steps also need to be taken to prevent theft and waste, and for the safe disposal of unwanted or out-of-date medicines (8). Inferior and fraudulent medicines are a problem, and lead to considerable waste.

Quality control and regulatory procedures need to be strengthened and enforced. The regulatory authority is the agency responsible for developing and implementing much of the legislation, regulations, standards, and specifications on medicines that ensure their quality, safety, and efficacy; together with accurate product information, advertising, and promotion materials (Zimbabwe). Specified standards and mechanisms for manufacturing practices, inspection and law enforcement; registration of medicines and supplies, registration/licensing of practitioners and premises; and inspections are required (South Africa) so that only authorized medicinal products are in circulation (Zimbabwe). Post-marketing surveillance and systems for reporting adverse drug reactions and quality defects have been introduced (Uganda, Zimbabwe).

Importantly, a strong public awareness is needed on appropriate handling and use of drugs and the associated hazards when these are not regulated, as well as the need for effective enforcement and strengthening of regulatory controls (Uganda). Substandard, ineffective or defective vaccines and medicines can enter a country as "gifts," as has happened during the Covid-19 pandemic (18).

Enabling Local Manufacture

Essential medicines have been the target for local manufacture, to promote national self-sufficiency in their production (Ghana, South Africa, Uganda, Zimbabwe). Addressing tariffs and taxes to manage prices is one important aspect, as well as establishing regulatory processes.

Data Collection

NMPs identify the need for greater data collection of sufficient quality for measuring and monitoring the burden of disease, need for services, the effectiveness of healthcare, and medicines and technologies and how they are used. For example, active monitoring and correction to fit with treatment guidelines is needed for prescribing behaviors (Ghana, South Africa, Uganda, Zimbabwe); hospital and district drug and therapeutic committees can provide guidelines and institute a feedback

system (Uganda); and data can be used to inform the prescribing and dispensing of antibiotics to reduce resistant microorganisms (19). Data on disease burden and infrastructure can also be used to inform health policy.

HEALTH TECHNOLOGY ASSESSMENT AND NATIONAL MEDICINES POLICIES

What Is Health Technology Assessment (HTA)

HTA is a multidisciplinary process that gathers information about the medical, social, economic, and ethical issues related to the use of a health technology (20, 21). Value judgements are made through multi-stakeholder appraisal committees as these are most likely to pick up unintended consequences of a technology. Each country can make its own philosophical decisions with a societal objective about the healthcare it provides (22). Civil society has an important place in HTA processes, as recognized by INAHTA, the International Network of Agencies for Health Technology Assessment (23) and as argued by Wale et al. (24). From a patient perspective, patients have a right to participate in the planning and delivery of their healthcare, where HTA determines the health services, procedures, and technologies available to them; as a way to build trust in the health system, add value to patients, and center on evidentiary contributions that patients can provide (24). From a methodological perspective, patients may be able to help HTA methodologies evolve, for example by seeking clinical trial outcomes that matter to patients, looking for different clinical trial designs, involving broader groups of people, and in following real world evidence (25).

Why HTA Is Important

Priority setting and funding are recognized as being value-laden with many factors, or criteria, of importance that extend beyond determination of cost-effectiveness. Because the various stakeholders have different priorities, evidence-informed deliberative processes as institutionalized in HTAs can provide transparency and the space to reflect and learn about the different societal values in the local context (26).

For priority setting to be fair, just distribution through a fair and accountable process is called for. In the African situation, the right to health can be seen as an obligation to be realized over time with dependency on resource availability. National strategies and plans of action are then based on the burden of disease across the entire population and obtained through a legitimate, participatory process. Transparency in prioritization is important, so that civil society and health planners can then advocate for accountability, additional resources, and for delivery of high priority services that provide considerable value (27).

How NMPs Can Promote HTA

HTA can provide a mechanism for transparent processes for evidence-informed assessment of the value of a medicine or technology leading to managed access to, distribution and rational use with informed reimbursement decisions specific to a country and its priorities in universal coverage of healthcare (20, 26). Good data collection and commitment of government to funding are needed.

The NMPs follow UHC principles as part of the United Nations health-related Sustainable Development Goals (SDG 3), where policy goals are to broaden health coverage to wider population groups; improve financial risk protection; and expand the types of health services people receive (11). Ensuring availability and access to affordable essential drugs in all parts of the country (Uganda), especially to the vulnerable segments of the population (Zimbabwe) is an important aspect of UHC. The first consideration of an NMP is basic essential medicines for all people, before addressing expensive medicines that benefit only a small proportion of the population. This priority is set above "the right to healthcare." Selection of medicines can also take into account the differing training and skills of the prescribers who are working at different levels of healthcare (see Ghana). These factors, as contained within NMPs, are therefore important to have in place for the fair and equitable introduction of HTA processes.

In 2003, Ghana became the first Sub-Saharan African nation to introduce a tax-funded National Health Insurance Scheme (NHIS). Ghana went on to include the concept of HTA within its 2017 NMP (13).

CASE STUDIES FOR INTRODUCTION OF HTA PROCESSES

Ghana—Case Study of HTA Using External Resources

In its NMP of 2017, the Republic of Ghana Ministry of Health recognized the potential of HTA to assist in identifying cost-effective health technologies for diagnosis, prevention, and treatment of health conditions. Use of HTA could provide a transparent process for evidence-informed assessment of the value of a medicine or technology and support reimbursement decisions (13). In 2021, Ghana launched its first strategy for HTA. This strategy extends from capacity development, topic selection, and methods guidelines to strategies for implementing HTA findings and assessing impact. It is linked by a strong governance framework (28). Over the last 10 years, the Center for Global Development in Europe (iDSI) built strong government and academic partnerships in Ghana to support government decision-making capacity so it could move "beyond aid" with long-term financial sustainability. The Norwegian Institute of Public Health joined the iDSI network in 2018, to further support this work (29). HTA has already demonstrated its value, for example in changing the formulation of amoxicillin, assessing the COVID-19 Vaccination Plan, and determining the cost-effectiveness of treatments for newly diagnosed hypertension (28). The principles of rational use of medicines are strongly evident in these activities, as promoted by WHO (17).

Case Study of Thailand as a LMIC That Has Successfully Developed Its Own HTA Program

The concept of incorporating HTA into health policy is relatively new to Africa. A well-documented internationally shared example of successfully initiating HTA processes in a middle income country has been set by Thailand (30). Thailand had well-trained medical practitioners through international partnerships, good healthcare infrastructure, and a national insurance scheme (established in 2001) to provide UHC (31). HTA provided a defined process in coverage decisions for high-cost medicines in the National List of Essential Medicines and to expand the Universal Coverage Scheme (UCS) benefits package. This was in response to increasing public expectations for access to more expensive medical services. Medicines reimbursement was important not just to provide essential medicines and ensure cost-containment, but to reimburse innovative, expensive medicines, and procedures that would add considerable value to healthcare. The HTA processes and methods were developed and adjusted over time. The first research projects, in 2000 and 2004, were joint programs coordinated and funded by Thai government organizations and international funding agencies. Burden of disease studies and priority setting were addressed (e.g., for HIV and rotavirus vaccinations, mental health, cardiovascular disease, diabetes, and road traffic injuries) (30). The government then went on to set up research bodies without international involvement. An HTA unit was established in 2002 focusing on standards of care and quality improvement in Thai top hospitals. In 2007, the unit became the Institute of Medical Research and Technology Assessment and was important for the development of clinical practice guidelines together with economic evaluation. In the same year, the Health Intervention and Technology Assessment Programme (HITAP) was established under the Thai Health Promotion Foundation. HITAP developed HTA and economic evaluation guidelines based on an extensive assessment of existing HTA processes in other countries (Australia, Canada, Denmark, Norway, Hungary, England, and Wales) (32). In Thailand, civil society groups, patient organizations and lay people (from the National Health Assembly) played a role in the prioritization and assessment of proposed health services to be reimbursed by the UCS. For example, in the introduction of innovative renal technologies and in high-cost cancer medications (30).

CONSUMER ENGAGEMENT IN LMICS

Importance of Consumer Engagement in NMPs and HTA—Patient Safety and Advocacy

The highlighted NMPs emphasize the importance of information on medicines for patients and the public, where "objective, relevant and practical information is important to health workers, patients and the general public." This is to enable improvements in the understanding of the place of medicines in healthcare. The NMPs stress that it is important everyone involved in over-the-counter sales know to handle medicines ethically and that they receive practical and relevant information on the correct use and storage of medicines, for safe, rational and effective use (Uganda, Zimbabwe).

Patient safety has received particular attention in WHO programs and the World Alliance for Patient Safety was launched in 2004. The Patients for Patient Safety global network was created in response to an initial WHO Patients for Patient Safety workshop in London in the following year (33). At this workshop, patients and professionals from 20 different countries including Africa were brought together to create a common vision, guiding principles, and commitment to positive engagement.

The International Alliance for Patient Organizations (IAPO) supports member patient advocacy groups in Africa (34) with participation extending to leadership roles. This has meant that patient advocates from Africa are in good standing with the international community of patient advocates and can play a strong role in promoting the regulatory infrastructure and management of medicines across Africa (10). Patient advocates are also involved in other global non-profit organizations such as the HTA International (HTAi) Patient and Citizen Involvement in HTA Interest group (35), the Professional Society for Health Economics and Outcomes Research (ISPOR) in health economics and outcomes research (36), and Cochrane for evidence informed healthcare (37). Adoption of civil society involvement provides a mechanism to strengthen the democratic legitimacy of the HTA process, and so decision-making. Such involvement can also lead to better decisions that reflect patients' experiences and values (38). Democratic legitimacy involves questions about where the data for an HTA comes from and how it is analyzed, and prioritizes inclusion rather than scientific rigor. Principles of accountability, fairness, representation, and transparency become important (39).

Stigma attached to diseases is an important aspect for the healthcare of individuals. Patient and community groups have traditionally provided community service delivery models of care, for example in Uganda by the National Organization for People Living with Hepatitis B and Uganda Alliance of Patients' Organizations (34).

Globalization with trade agreements, pharmaceutical company activities and digital technologies contribute to the spread of knowledge about new and promising technologies. This can place pressure on often fragile health systems with limited infrastructure, and frequent absence of government-funded national health insurance schemes. If the State does not have a civil society organization engagement framework set in law, policy, or practice standards, then patient engagement in healthcare decision-making may be largely absent and is a "democratic deficit" (40, 41). Yet mobile technologies and access to the internet mean that African people can be pro-active in monitoring their health and sharing their health information with community health workers and pharmacists to reduce the burden on overstretched, understaffed health centers (42).

It may be important for Africa with its complex societies in terms of gender, tribal aspects, ethnicity, language, etc. to take an active interest in patient preference studies. Research is ongoing to provide understanding of how patient perspectives can be captured with patient preference data for use in

decision-making about new medicines and technologies (43–45). Such scientifically-derived quantitative evidence could align with the methodological values of HTA professionals. The European Union Innovative Medicines Initiative (IMI) PREFER project submitted a framework informing objectives, design and conduct, and reporting of patient preference studies to the European Medicines Agency to provide an assessment (46). Its draft opinion states that a case-by-case decision would be needed on the weight put on specific results from such studies (47). The National Institute for Health and Care Excellence (NICE) in the UK undertook a project funded by the patient charity Myeloma UK (2016–2018) and suggested there is a clear scope for better use of quantitative patient preference studies (44).

Government Initiatives That Have Encouraged Consumer and Community Participation in LMICs

In 2007, Thailand established an autonomous government agency called the National Health Commission Office (NHCO) under the National Health Act. This agency enlists patient groups and civil society groups registered as legal entities and represented in the National Health Commission to follow participatory public policy processes. As an example, when prioritizing services for extension of the UCS benefit package in 2009/2010, civil society, patient groups, and lay people from provincial networks of the National Health Assembly participated. Interventions included setting fees, an HIV/AIDS program, a chronic diseases package and a psychosis package (30).

Thailand has also run a village health volunteer program for decades now to strengthen primary healthcare through health education and self-care support, community, and long-term care (42).

POSSIBLE WAYS FORWARD

In establishing a structure or organization to undertake HTAs, sustainable funding, governance, and accountability are prime factors. Conflicts of interest need to be managed and legitimate processes established (26, 31). People undertaking the HTAs need to have the required skills and competencies, and recommendations need to be implemented. In this perspective we have given an example of where external bodies have helped to establish HTA practices in Ghana. The Thai HTA body founded the active HTAsiaLink Network to undertake knowledge sharing and best practices of HTA in the Asia-Pacific region (48). Network members are also members of INAHTA, with its statement on the importance of patient involvement in HTAs (23).

The IAPO first Virtual African Patients Congress brought IAPO's African patient organization membership together with high-level African healthcare stakeholders including regulators, policy makers and others to "share their vision and experience on how we can build back better African health systems after the pandemic" (10). The African Medicines Agency (AMA), as of November 2021, as a single centralizing regulatory body for medicines in Africa is strongly supported. It is hoped that the activities of the AMA can become patient-centric and that it can build patient engagement into its regulatory framework by applying laws, policies, practices, and standards. Building expertise and capacity is a vital part of the vision of the AMA (49, 50). For some, it is important for medical regulators to involve patients and the public across the spectrum of their work (49, 51). Having patient advocates at the discussion table, as occurred with the IAPO African Patients Congress (9), is an important step in African countries working together to incorporate patient values in healthcare. By being involved, patient and community groups and civil society are acknowledged as having a role in gaining recognition of the AMA and other activities to ensure accessibility to high quality, affordable medicines and to promote democratic legitimacy in setting the health policy agenda.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Solving the Evidence Interpretability Crisis in Health Technology Assessment: A Role for Mechanistic Models?

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Health technology assessment (HTA) aims to be a systematic, transparent, unbiased synthesis of clinical efficacy, safety, and value of medical products (MPs) to help policymakers, payers, clinicians, and industry to make informed decisions. The evidence available for HTA has gaps—impeding timely prediction of the individual long-term effect in real clinical practice. Also, appraisal of an MP needs cross-stakeholder communication and engagement. Both aspects may benefit from extended use of modeling and simulation. Modeling is used in HTA for data-synthesis and health-economic projections. In parallel, regulatory consideration of model informed drug development (MIDD) has brought attention to mechanistic modeling techniques that could in fact be relevant for HTA. The ability to extrapolate and generate personalized predictions renders the mechanistic MIDD approaches suitable to support translation between clinical trial data into real-world evidence. In this perspective, we therefore discuss concrete examples of how mechanistic models could address HTA-related questions. We shed light on different stakeholder's contributions and needs in the appraisal phase and suggest how mechanistic modeling strategies and reporting can contribute to this effort. There are still barriers dissecting the HTA space and the clinical development space with regard to modeling: lack of an adapted model validation framework for decision-making process, inconsistent and unclear support by stakeholders, limited generalizable use cases, and absence of appropriate incentives. To address this challenge, we suggest to intensify the collaboration between competent authorities, drug developers and modelers with the aim to implement mechanistic models central in the evidence generation, synthesis, and appraisal of HTA so that the totality of mechanistic and clinical evidence can be leveraged by all relevant stakeholders.

Keywords: modeling and simulation (M&S), mechanistic evidence, drug development, health technology assessment (HTA), stakeholder engagement (SE), mechanistic models

INTRODUCTION

Health technology assessment (HTA) is a systematic and multidisciplinary process that summarizes medical evidence, social and economic impact, and ethical issues related to the use of health technology. HTA addresses both the direct and intended effects of this technology, as well as its indirect and unintended consequences—with the goal of informing decision making. A major feature of the collective output of a HTA process is the reimbursement by the health insurance system of the medical product (MP).

In general, two levels of decision-making regarding health care should be informed by HTA: (1) for the community—is the MP worth giving to the population, and could it be more or less beneficial for a group in the population? (2) for an individual: will a particular patient benefit from the MP, and if yes to what extent?

HTA seeks to couple the available evidence on the MP and the disease with the decision-making process itself, and thus has similarities to evidence-based health care and evidence-based policymaking (1). By evidence, one should understand a comprehensive record of knowledge and data collected in clinical trials (of which randomized, placebo-controlled studies are the gold standard), observational studies and from various sources relating to patient health status and/or the routine delivery of health care (often referred to as "real-world data," RWD). One could say that HTA interprets clinical data from a real-world perspective by considering the realistic epidemiology of the disease and the full range of standard of care options (available to the population of interest). For a given MP (we focus on new drugs in this Perspective), the first round of assessment occurs during the review of the market authorization (MA) application by the regulators, e.g., FDA (Food and Drug Administration) or EMA (European Medicines Agency) for safety and efficacy. Given that the evidence included in these applications is generated throughout several years of development, key stakeholders could and should synergize and could streamline evidence generation and assessment from the beginning (2). Non-RCT data such as observational study data or RWD might bear relevant and additional information about safety, effectiveness, and cost effectiveness of MPs at potentially a larger scale. However, issues with identification, access, quality, representativeness, and heterogeneity of such data are limiting their practical applicability in HTA (3, 4).

The COVID-19 pandemic has disrupted global healthcare systems and created significant challenges for the HTA and payer communities (5). The COVID-19 pandemic has clearly shown where evidence generation, synthesis, assessment, and decision making are limited: (a) the typical bench-to-bedside timeframes of several years are simply unacceptable in a pandemic context; (b) clinical trial evidence collected in "emergency mode" suffers from increased uncertainty regarding the expected treatment effect, outcomes and costs (6); (c) the diversity of national policies and their frequent changes make it hard to come to conclusions on ethical and societal issues and raise barriers for patients to fully capture and understand the impact of a new MP on their life.

Especially in light of the COVID-19 pandemic, the importance of the assessment for the individual cannot be underestimated. While some patients do not suffer from any symptoms, others do not survive, or are affected on long timescales. Clinical data on COVID-19 prophylaxis and treatment currently under-represents the individual course of the disease due to the diversity and time dependency of the interactions between the virus and the patients' bodies. Here, the inherent limitation of HTA—being centered around population-based approaches—is aggravated. Issues related to better guiding economic evaluation of personalized medicine interventions—e.g., how study questions are developed, how populations are characterized, how comparators are defined, how effectiveness is evaluated, how outcomes are valued and how resources are measured (7)—need urgently to be addressed for the assessment of MPs related to COVID-19.

The COVID-19 pandemic has also raised the bar for communication around HTA. There has been divergence of opinion among international HTA agencies on how to deal with evidence for early COVID-19 treatments (8). This divergence and lack of transparency about the reasoning behind the assessments during this unsettling period have triggered public unease and skepticism with HTA as a whole.

As a response to the urgency to address these challenges, we wish to advocate using mechanistic models to bridge clinical MP development and HTA thanks to their capability for evidence generation, synthesis, and stakeholder communication alike.

CHALLENGES FOR HEALTH TECHNOLOGY ASSESSMENT

A key issue for HTA of a new MP is the number of limitations regarding the representativeness and validity of the evidence that is available. For conclusions useful for patients and public health, more quantitative knowledge and valid answers to questions need to be found (**Table 1**).

Randomized Clinical Trials (RCTs) Deliver a Binary Answer to a Binary Question

A first reason for the limited use of data generated during development lies in the results provided by randomized clinical trials (RCT) which are the gold standard for clinical evidence. An RCT is an instrument built to determine if the new treatment is effective or not by statistical testing. The frequentist inference paradigm (26) is still today's standard method in RCT despite the advent of innovative trial designs and analysis techniques [i.e., Bayesian (27)] but can limit drastically the interpretation of the efficacy tested in the trial (26, 28). In addition, the fact that statistical models are not designed to look for causality—but only to identify correlations available in the data—prevents a quantitative appraisal of the MP efficacy tailored to patient profile (20).

RCT Data Reflects Benefit of the Population and Not of the Individual

A second limitation in HTA is the fact that currently population (and sometimes stratified) medicine is pursued during clinical

TABLE 1 | Examples of how published (mechanistic) models rooted in the clinical development space (model informed drug development, MIDD) could address uncertainties in new medicinal product assessment reports.

Uncertainty not completely addressed in competent authority assessment report	Example use of MIDD relevant to address uncertainty potentially also during HTA
What is the optimal dosage in the clinical context?	Physiologically based pharmacokinetic models can investigate dosing-regimens relevant for regulatory review and product labels (9) and can also mimic real-life adherence to prescribed treatment regimens (see also below) or pharmacology-relevant characteristics of special populations as well as drug-drug interactions.
What is the duration of the effectiveness, especially with chronic use of a treatment?	Mechanistic models can predict the long-term disease progression by extrapolation of shorter-term findings under the constraints of how the components of the system function (and these constraints convey biological plausibility by design). An example is the use of a mechanism-based disease progression model for comparison of long-term effects of pioglitazone, metformin, and gliclazide on disease processes underlying Type 2 Diabetes Mellitus (10). Another example is prediction of long-term outcomes by short-term marker data as demonstrated by a semi-mechanistic approach in context of osteoporosis treatment (11).
What is the efficacy for relevant clinical outcomes?	Mechanistic models combined with pharmacometric approaches can translate findings for one outcome to a range of other outcomes. An example of survival modeling on the back of a mechanistic description is the modeling framework for CD19-Specific CAR-T cell immunotherapy using a quantitative systems pharmacology model (12).
What is the size of the clinical effect dependent on patient characteristics and extrinsic factors?	Data-driven modeling techniques can capture correlation within clinical data. Describing the clinical effect of a drug can also be based on mechanistic considerations. Such models either (a) link disease phenotypes to increasingly granular mathematical representations of pathophysiologic processes (top-down approach) or (b) derive functional, computable cellular networks from the molecular building blocks of genes and proteins to elucidate the impact of pathologic or therapeutic alterations on network operating states and hence clinical phenotype (bottom-up) [see (13)]. In this way, functional relationships can explain the found correlations and can be used for quantitative analysis of the effect size and the causality dependent on intrinsic and extrinsic factors.
What is the difference in effect when compared head-to-head to other comparators?	Mechanistic modeling is a commonly used tool to explore treatment combinations in immuno-oncology [see for example (14)] which can enable head-to-head comparisons. A mechanistic approach with clinical trial simulation can provide model-based meta-analysis which can ameliorate indirect comparison of clinical data (15).
What is the efficacy compared to placebo or the standard of care, when controlled studies are hard to conduct?	For comparative effectiveness research, data from a control arm is needed. When such control arm is unfeasible (for example because of ethical reasons), external or synthetic control data may be an avenue to put uncontrolled clinical data into a controlled setting, but mitigation of the risk of bias needs adjustment techniques. Mechanistic modeling can quantitatively predict the effect of an intervention on a clinical outcome as a function of patient characteristics and extrinsic factors, on a single patient level. These features render mechanistic models promising to set up unbiased synthetic control arms [SCA, see (16)].
What is the effect of real-life compliance on efficacy?	Explicit simulation of administration adherence can be coupled with pharmacokinetic models. One example is the simulation of adherence patterns using Markov Chains for trial design (17, 18).
What is the distribution of responders in the target population?	Predicting individual response to treatments needs the convergence of large-scale mechanistic models [e.g., in cancer pathways (19)], appropriate responder profiling framework and cost-effectiveness analysis [for example the Effect Model approach, see (20, 21)]
What is the size of the benefit at the population level?	Mechanistic models providing clinical outcome estimates can be used on the entire population level to predict effectiveness, given that adapted metrics are used (22)
What is the long-term safety and what impact does the occurrence of rare side effects have over long-term use?	The combination of quantitative systems toxicity (23) with organ (e.g., cardiac, and renal) impairment (24) in frame of disease progression modeling (25) can be used to simulate long term safety aspects of a treatment from a mechanistic point of view

Emphasis is put on mechanistic models.

development while for HTA, the benefit for individual patient (groups) becomes important. RCTs, done either separately for different strata for the population or analyzed for different subgroups of one larger study population are currently the only tool available to "individualize" a MP efficacy estimate. As it is the central focus of an RCT to robustly estimate the average effect in a given population, cannot be obtained easily and hence, detailed information at patient level and the mean estimated effect is "applied equally" to each patient. Frequently, patients enrolled during clinical development are not entirely representative of the future target population because of the way they are selected to enter the trials. And they are furthermore limited in number and diversity. Reliably quantifying the effect for individuals from this evidence is therefore limited as well.

The advent of personalized medicine puts the "mean efficacy" approach in question (7) and calls for a paradigm shift of how efficacy should be considered for market authorization (MA)—and market access.

High Quality Data Exceeding the Scope of Market Authorization Is Scarce

For sponsors, there are increased barriers to conducting randomized trials after registration. Availability of a treatment with proven efficacy may pose ethical problems for placebo-controlled trials. Additional information about the effect of a treatment often needs to rely on observational studies and RWD (for example registers, patient records). The fact that RWD contains routinely collected information and low accessibility but

high heterogeneity of data (29, 30) does not easily reveal the detailed and true epidemiological status of a disease or the effect of an intervention in the population. Even with the additional use of RWD, it remains difficult to derive an overview of the long-term and real-life impact in the clinical practice necessary for the HTA exercise.

In summary, gold-standard evidence for HTA (RCTs) can be regarded as more qualitative than quantitative, it has a domain of validity restricted to the context tested in clinical trials during clinical development and does not answer a number of important questions (see **Table 1**). It is not always possible to collect enough high-quality observational data and RWD to fill the gaps. In view of these challenges, and even more so when there is a strong, urgent, unmet therapeutic need (as today—facing the COVID-19 pandemic), HTA agencies are faced with a difficult dilemma: They can assess and position themselves on the basis of uncertain evidence (risk of misjudgement) or wait for more solid evidence (risk of delaying the access to a potentially effective product for patients with progressive disease or in treatment failure). This situation advocates to make better use of the "totality of evidence" generated during development.

ADVENT OF THE MECHANISTIC APPROACH IN MODEL INFORMED DRUG DEVELOPMENT

Model-informed drug development (MIDD) applies drug exposure-based, (systems) biological and statistical models derived from preclinical and clinical data sources to inform drug development and decision-making (31). It integrates information from diverse data sources to decrease uncertainty and lower failure rates, and to develop information that cannot or would not be generated experimentally. The most widespread fields of application within MIDD are pharmacokinetics and pharmacodynamics and dose-response relationship modeling for dosing-regimen explorations as well as trial simulation for design optimization.

Within MIDD and regulatory decision making, a new set of models is emerging (32, 33). These models are based on knowledge with theoretical rules describing known mechanisms (called mechanistic models[1]). Within the family of mechanistic models physiologically based pharmacokinetic modeling (PBPK) adopts a mechanistic approach to describe what the body does to the drug and quantitative systems pharmacology (QSP) models aspire to capture what the drug does to the marker, organ, or clinical outcome. As opposed to data driven models, mechanistic ones describe known or hypothesized mechanisms at a smaller scale so that the higher scale behavior emerges (34). In most mechanistic models the equations describe functional relationships between molecules, cells, or organs. The choice of the used equations and their parameters is informed through systematically reviewing and curating the available biomedical knowledge about the process of interest, and in turn, each component of the model (variable state, parameter, and equation) can be unequivocally justified by a corresponding piece of knowledge in the literature (or other considered source of knowledge)[1]. The equations often come in the form of systems of ordinary differential equations (ODEs) that can describe coupled dynamics of the entities in the biological system of interest (but also other approaches such as partial differential equation systems or agent-based models exist). The covered composition of biological entities and scale of the description such as molecules, cells, organs, or the whole organism can vary depending on the context (35–37) and thereby define the specific scope and limitations of the model. Annotation and metadata for this knowledge can comprise additional information, for example a collaboratively curated or consensus strength of evidence and ontologies. These features can provide biological plausibility to those models by design and thus be used to rationalize, explain, and translate representative or individual clinical findings based on the (often large) body of mechanistic knowledge used in the model. Where parameters cannot informed by knowledge and remain unknown, heterogenous (*in vitro*, preclinical, omics, clinical) data can be used for (algorithmic) calibration (38).

The adoption and use of mechanistic models in model informed drug development and especially in regulatory decision making requires to establish their credibility through verification, validation and uncertainty quantification for which existing guidelines need to be adopted by modelers and more specific guidance issued by regulators (34).

In response to the COVID-19 pandemic, mechanistic models have been put forward to guide antiviral drug repurposing (39) and vaccine development (40), showing that such models can synthesize and translate the body of biological knowledge into a clinically relevant setting in a short time frame.

Mechanistic models are associated with a Virtual Population (VPop) to introduce interpatient variability. A VPop is a set of virtual patients, each one being characterized by its own set of descriptors (model parameters values) that follow pre-defined joint distributions (41–43). Simulations can be conducted in varying scenarios (such as different treatment regimens) according to a simulation protocol that defines the entire *in silic*o clinical trial. These *in silico* trials produce digital evidence to explain, complement or partially replace *in vivo* clinical trials for drug development (44, 45). Running mechanistic model based *in silico* trials with a theoretically infinite number of patients can support evidence in rare settings and place population-level results in relation to individual simulated patients. The mechanistic and individual nature of the underlying model further allows one to allocate "clones" of the same patients in different arms and simulation scenarios corresponding to idealized clinical trial settings. In this way, effectiveness can be rationalized through tracing it to impacting and confounding factors.

Mechanistic models thus can bring biological plausibility, equity of clinical and mechanistic evidence as well as individual predictions (similar to idealized RCT settings) to the table of evidence synthesis and generation.

[1]Please note that, depending on the availability of knowledge, mechanistic modeling approaches may combine a fully mechanistic design for well-known processes with simplifications and assumptions or more phenomenological approaches where knowledge gaps exist. Therefore, the more general term Knowledge-Based Models, (KBM) might be more accurate than "mechanistic models," but the latter is more widely used.

MODELING IN HEALTH TECHNOLOGY ASSESSMENT

Modeling in HTA is conducted during (1) the evidence synthesis phase and (2) economic impact assessment, mostly through data-driven modeling approaches. Mechanistic models are still underrepresented in this field but coming of age.

For evidence synthesis, different data-driven modeling approaches are commonly used. Pairwise and network meta-analyses (NMA) (46) using fixed effect and random effects models are tools to synthesize evidence from randomized controlled trials. NMA allows for comparisons that have not been directly obtained in head-to-head trials but comes with methodological challenges. NMA relies on the assumption that the analyzed studies are similar in all factors affecting the relative effects, which can lead to biased results. Moreover, these types of models are often limited in their data source scope. To address this issue, a technique combining NMA with quantitative modeling of effect modifiers (e.g., doses) has become available—utilizing the "totality of evidence" (47). Such "model-based" NMA can mimic randomization and allows estimation and predictions for multiple agents and a range of doses, using plausible physiological dose-response models (48). Additional to data from RCTs, data from observational studies is increasingly used in the evidence synthesis, which, however, lacks an unbiased control arm and techniques for reducing biases need to be applied (49).

For extrapolating a clinical effect into longer-term economic impact there exists quite a variety of methods, which are used for HTA and can be classified as cost-benefit analysis, cost-effectiveness analysis, and cost-utility analysis (50, 51). Simple graph-based decision trees, Markov models [suited for diseases that involve an ongoing risk (52)] or more involved discrete event simulation (DES) (53) and agent-based models (54) are frequently used for data analysis, classification and interpolation and extrapolation in time. The data fed into these models, however, is incomplete due to the limited evidence generated in clinical development (see open questions in **Table 1**).

Mechanistic models can bridge the gap between development and HTA. Given that validation can establish the credibility of a model for regulatory decision making, exploration of a much larger number of situations than in RCTs (with different patient subgroups, treatment compliance or comparators for instance) might be feasible. Such digital evidence supporting RCT data alleviates several difficulties such as power, representativeness, costs to run the trials, and ethical issues. For the consideration of such evidence in HTA one should consider the following unique benefits of mechanistic model that statistical ones cannot provide. First, mechanistic models possess biological plausibility by design—using biological, chemical, and physical processes as "blueprint"—and are therefore well suited for extrapolations. Second, the VPop can be set up to assess the very same patient under various conditions and scenarios (such as treatment arms) which corresponds to an idealized crossover design and allows to assess clinical benefit for every individual.

A concrete list of examples of how mechanistic models can address unanswered questions left in the MA dossier is given in **Table 1**. In summary an individual estimate of the (real and long-term) benefit-risk ratio using mechanistic models and adequate metrics (21, 22) feed a precise estimate of the costs of treatment for better health economic projections.

MODELING FOR STAKEHOLDER ENGAGEMENT

HTA is a multi-stakeholder activity that should shed light on more facets of an MP than just a technical analysis. Especially in the appraisal phase, "complex calculations, arbitrary assumptions, debatable choices of whose perspectives to pursue, difficult-to-understand methods, research designs and underlying philosophy/concepts, and time-consuming processes" are at risk of narrowing the HTA findings (55). It has therefore become clear that a diverse set of views need to be captured, consulted, and considered. At the same time, different stakeholders have unique needs that must be addressed before these stakeholders can position themselves. It is to note that recently the importance of engaging patients and patient groups in HTA has been emphasized (56) and there are examples of such engagement in several countries. Nevertheless, systematic involvement from beginning to end of the HTA process [not only during the appraisal stage as currently often the practice (57)] is still an ongoing effort (58). Apart from the need to include different stakeholder groups, there is no consensus what role each stakeholder group should assume in overall decision-making process ranging from information, consultation, participation in the debate, co-decision, as sole decision maker (59). Despite this ongoing debate on the exact role, better mutual understanding, communication, and engagement are sought, all centered around the available evidence. Modeling and simulation and especially mechanistic models may be used as a tool for stakeholder engagement apart from their capability to create (digital) evidence and synthesize data. There is an example from the literature underlining that participation can be achieved by applying an adapted conceptual framework for the modeling and simulation process [see for example (60)]. For this reason, we attempt a mapping of the differences between roles and contributions of stakeholders with specific needs and a suggested use of mechanistic models in **Table 2**.

There are still barriers dissecting modeling in the HTA space and modeling in the clinical development space. These barriers are conceptually similar to the known barriers to bring HTA to policy making (65). Specific barriers delaying the use of mechanistic models in HTA are (i) the lack of an adapted model validation framework for decision-making process in both contexts (MA and HTA), (ii) inconsistent and unclear support of mechanistic models by the involved stakeholders (competent authorities, and stakeholders involved in HTA likewise), (iii) limited use cases with relevance to clinical development and HTA alike, and (iv) absence of appropriate incentives to use mechanistic modeling throughout the MP development lifecycle.

TABLE 2 | List of different Stakeholder groups increasingly involved in the appraisal stage of HTA with dedicated contribution, special needs (to understand and capture a drug's mechanism, effect, role, or impact) and example of how mechanistic modeling can help to address this need and fill persistent gaps.

Stakeholder group	Contribution to HTA	Needs	Role of mechanistic models for increasing stakeholder involvement
Individual patients or disease-specific citizen and/or patient organizations/associations or caregiver and family member groups	First-hand experiential knowledge of living with a particular health condition; experience with the health technology under assessment, or currently available technologies, the use of associated health services, and associated benefits, risks, and side effects	Needs to understand the impact of a new MP on personal and individual health status, personal risks, and benefits	Establish plausibility and interactivity of clinical decision-making Highlight potential individual consequences from clinical decision making Highlight individual patient contribution to outcomes (e.g., compliance)
Citizen and health system user organizations not specific to any condition or disease. Public in general	May lack knowledge about disease or health technology in question but can assess transparency, legitimacy, and fairness in decision making (61)	Needs to understand reasoning in the decision-making process	Establish plausibility and interactivity of the policy decision-making
Healthcare professionals Organizations of healthcare professionals	Gather expertise on clinical aspects regarding: the disease/condition; medical needs; available therapies; the technology under assessment	Needs to be convinced about the new health technology being the best therapeutic approach to be delivered to a patient.	Provide clinically relevant scenarios of HT impact on outcomes, among other comparator approaches
	Identify clinically relevant patient population (and/or subgroups), comparators, thresholds for improvement	Needs to decide, diagnose, or prescribe based on large and complex scientific knowledge	Provide a comprehensive view of all the available scientific knowledge
	Gather information on clinically relevant outcomes including possible neglected outcomes		
	Gaining further information on the importance of outcomes from a healthcare professional point of view (62)		
Policymakers	Can judge the expected benefit for healthcare on a national or regional level given the specific political background (63)	Need to estimate a new treatment impact on a national or regional level	Provide trustworthy estimation of a new treatment benefit on a specific population where little data is available
Payers	Contribute expertise on reimbursement/coverage decisions Can highlight specific national or regional economic background	Need to estimate a new treatment impact on a national or regional level	Provide trustworthy estimation of a new treatment benefit on a specific population where little data is available
Companies and associations producing health technologies	Technology manufacturers can take part (as peers) in all discussions and meetings about contributed data to clarify concerns and provide additional information to support coverage of their products (64).	Needs to understand and rationalize questions and concerns vs. specific available data	Show how technology manufacturer's data fits into the overall evidence Highlight technology and product specific properties with respect to reference
Academics	Provide cross-disciplinary scientific feedback from public health, economics, ethics, and social sciences	Needs to understand the bigger picture of HT	Provide information for other models and assessments

The earlier a dedicated modeling strategy will be put in place the greater will be the demonstrated ability to predict a drug's impact, robustness, and credibility. Bringing mechanistic modeling to HTA, and thus the availability of this tool for the stakeholders requires, however, that drug developers, competent authorities and modelers anticipate the use in HTA.

While **drug developers** could generate more HTA-relevant data during Phase III, the resulting pivotal trials would be more complex and risk missing the statistical target. Drug developers should therefore consider mechanistic models to bridge this gap and report HTA-relevant modeling outcomes, validated with Phase III results.

Competent authorities will have a special role in facilitating model-based stakeholder engagement. They should issue more precise and dedicated guidance so that more modeling is included in MA. They should intensify the reporting of mechanistic modeling studies in benefit-risk assessment reports.

The modeler needs to embrace the fact that non-experts will also be exposed to the (potentially complex) model and its results. There is a lot of work being done concerning the communication and reporting of clinical trial results to patients and the public which are also applicable for simulated trials. There are EU Commission recommendations on the content of a lay summary

(wording and layout) its development and dissemination—Good Lay Summary Practice (66). Communication of complex modeling results could profit from adopting such good practice.

CONCLUSION

The immediate and urgent unmet need for interventions and prophylaxis during the COVID-19 pandemic has suggested that drugs backed up by little empirical evidence (compared to the non-pandemic context), but a strong mechanistic background can be approved. The implications of this paradigm shift for HTA still need to be fully understood. In this article, we have advocated that mechanistic models can be used to reproduce, support and extrapolate clinical trials and could constitute a new type of evidence. Mechanistic models can provide causal and quantitative links between patient characteristics, personalized/realistic drug regimen or other extrinsic factors and individual benefit—under consideration of alternative treatment scenarios. They can therefore help to overcome barriers for a more quantitative appraisal of clinical data in HTA and they should also be considered to inform and educate special populations and individuals from a bottom-up perspective. Generation and uptake of *in silico* evidence will need more work of modelers, drug developers, and regulators, who will need to endorse and guide the use of mechanistic models early and consequently in the development process. Likewise, special attention will have to be paid to convey the totality of evidence to different stakeholder groups for empowering them to judge and formulate their specific viewpoint on the MP.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

EC, J-PB, AK, EP, JM, and RK wrote the manuscript. All authors discussed and reviewed the manuscript.

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Brazilian breast cancer patient-reported outcomes: What really matters for these women

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Introduction: Patient-Reported Outcomes (PRO) are directly reported by the patient without interpretation of the patient's response by a clinician or anyone else and pertains to the patient's health, quality of life, or functional status associated with health care or treatment. It can provide patients' perspectives regarding treatment benefit and harm beyond survival and are often the outcomes of most importance to patients. This study aims to describe and analyze outcomes reported by Brazilian women diagnosed with breast cancer and rank the most important attributes for these patients.
Methods: Observational descriptive study composed of exploratory interviews followed by online questionnaires applied to a convenience sample of women diagnosed with breast cancer.
Results: Twelve women were interviewed to explore the main outcomes and preferences about their treatments, such as the most common side effects and the most impacted aspects of life after diagnosis and BC treatment. Psychological, emotional, and sexual impacts were frequently described as impacted aspects. Fifty-three women, from all the five Brazilian regions, answered the online questionnaire. Following an order of importance ranking, the following outcomes were chosen, respectively: overall survival, progression-free survival; and quality of life. The treatment effects that were considered less important, among this sample, were pain and adverse events.
Conclusions: Thinking about expanding the therapeutic quality of users, it is essential to take into account the experiences of patients. PRO is a trend in current research to achieve this goal, in order to influence the decisions of HTA agencies about the importance of valuing outcomes that affect patients' lives.

KEYWORDS

patient-reported outcomes, PRO, PROs, patient preferences, preference study, breast cancer, patient perspective, patient experience

Introduction

Breast cancer has been a major public health problem. It is the second most incident cancer in the world and the most prevalent in women, besides being the second worldwide leading cause of cancer mortality (1).

Data from 1980 to 2006 showed that breast cancer mortality has been increased in all five major geographic regions of Brazil (2). Only in 2019, the Brazilian Mortality Information System recorded 18,296 deaths in women due to breast cancer, the principal cause of death from cancer in Brazilian women. Estimates for each 2020–2022 period indicate that there will be about 66 thousand new cases in the country. It is noteworthy that mortality rates are strongly related to access to health services and the quality of care that is offered to women (3).

As therapeutic options for breast cancer, primary tumor surgery, assessment of axillary involvement and radiotherapy as a form of local treatment and systemic drug treatment, which consists of chemotherapy and hormone therapy (4) In cases of resistance, new therapeutic options are used. One of these options is a combination of CDK4/6 inhibitors in combination with hormone therapy, which has been shown to be effective in women with advanced breast cancer negative for human epidermal growth factor receptor 2 (HER2), positive hormone receptor (HR+) (5).

In the Brazilian Public Health System, the current clinical guidelines recommend only hormone therapy as the first-line therapy for postmenopausal women with advanced luminal BC (6). However, international guidelines recommend adding CDK 4/6 inhibitors (such as Abemaciclib, Palbociclib, or Ribociclib) in the first-line therapy (7), since an increase in overall survival (OS) and progression-free survival (PFS) have been demonstrated in pivotal studies using these drugs in advanced luminal breast cancer (BC) (8–14).

OS has long been the gold standard outcome in establishing the efficacy of oncology therapies and PFS, defined in clinical trials as the time from randomization until first evidence of tumor progression or death from any cause, is commonly used as a surrogate endpoint, which has been questioned by some cancer researchers, often without an evaluation of patient preferences (15).

The patient experience has played an increasingly important role in clinical research since it is now understood that a whole system, such as a patient-centered approach, is required for a thorough assessment of the impact of therapy and care (16). In the last decade, the focus on the patient has become a key concept in research (17) and several health technology assessment (HTA) agencies promote patient engagement in the decision-making process as well (18).

Patient-Reported Outcomes (PRO) are directly reported by the patient without interpretation of the patient's response by a clinician or anyone else and pertains to the patient's health, quality of life, or functional status associated with health care or treatment (19). PRO instruments can provide patients' perspectives regarding treatment benefit and harm, directly measure treatment benefit and harm beyond survival, and are often the outcomes of most importance to patients. PROs can be used either as a secondary outcome of a study, to complement primary outcomes, such as survival rates, or as a primary outcome, when there is no objective outcome measurement (16).

According to an investigation about how inclusion of PRO evidence has evolved and influenced recommendations by HTA agencies (G-BA, HAS, NICE and SMC), 72% of the drug indication combinations included PRO data in one or more submissions. It shows that, however it is not yet a standard practice, HTA agencies tend to value the submission of PRO data and it can have a positive influence on recommendations (20).

In Brazil, Progress-free survival (PFS) is considered a substitute outcome in the guidelines for the treatment of breast carcinoma, which means, a PFS is not considered an important factor in this decisive process of incorporating a drug as an option in the Brazilian public health system (SUS) (6). However, based on consideration of patient preferences in the decision-making process, agencies such as the Canadian Agency for Drugs and Technologies in Health (CADTH), National Institute for Clinical Excellence (NICE), and the Scottish Medicine Consortium (SMC) have indicated that PFS is an important outcome for breast cancer patients, as it allows them to maintain their usual activities for a longer period. In addition, it was identified that patients would be willing to accept adverse events resulting from endocrine therapy so that they could postpone the need for chemotherapy, which is associated with higher toxicity and decreased quality of life than endocrine therapy. These HTA agencies seem to consider PFS in decision making, since all of them have approved drugs associated with PFS gain, such as CDK inhibitors.

In this way, the influence of patient participation in the decisions of HTA agencies is evident. Therefore, the present study aims to identify the main relevant outcomes for patients with breast cancer in Brazil, as well as to describe and rank important attributes and outcomes for these patients.

Materials and methods

This is an observational study composed of exploratory interviews followed by online questionnaires applied to a convenience sample of women diagnosed with breast cancer. The recruitment was carried out virtually between June and October 2020, through an online form, released by the research team in partnership with patients support Non-Governmental Organizations (NGOs), which are "*Oncoguia*", "*Recomeçar*", "*Zen Cancer*" and "*Colabore com o futuro*". The recruitment form received 46 responses. The following inclusion criteria was established: Brazilian women diagnosed with breast cancer who already have been or were being treated for breast cancer. After this initial recruitment, we firstly invited 29 women that answered the recruitment form and completed the inclusion criteria to be part of this study.

Data collection occurred first through individual exploratory interviews conducted by a trained researcher over the phone and lasted for approximately 30 min. The aim of the interviews was to capture important outcomes, preferences, and other results from patients, with the potential to provide insights that could help to answer the questions of this research. Twelve women were interviewed using a convenience strategy determined by theoretical saturation of the discourses related to the outcomes of the disease and treatment.

Subsequently, an online questionnaire was applied to the interviewed women and other patients that preferred to participate only in this phase of the study. The questionnaires were sent to the same patients who participated in the interviews and the NGOs cited above also helped to spread the survey among other breast cancer patients. The aim of this second phase was to classify and rank the attributes and outcomes previously identified in the interviews, in addition, to explore more the ethical, social, and patient aspects of this disease and its treatment from the perspective of the Brazilian breast cancer patients'.

The semi-structured interview questionnaire (Questionnaire 1) was developed considering the literature on the topic and the expertise of specialists, with the objective of collecting reports of patients' experiences and preferences, about important attributes and the classification of these. The online questionnaire (Questionnaire 2) was elaborated with close-ended questions using multiple-choice questions to measure Quality of Life and a Likert scale to rank the attributes and outcomes found in the conducted interviews.

All data were collected between September and November 2020. All participants provided informed consent prior to their participation.

To analyze the speeches of the interviews, a verbatim transcript was carried out in full, and the data of the interviewees were anonymized, using only the initials and thematic analysis (21). The thematic analysis is a qualitative analysis technique characterized by flexibility, as it is essentially independent of a specific theory or epistemology and can be applied with a variety of theoretical and epistemological approaches. The content analysis was peer review by two researchers of the team.

Results

Twelve women were interviewed in September 2020. They were from different Brazilian cities in the Southeast Region (São Paulo, SP; Rio de Janeiro, RJ; and Minas Gerais, MG), and in the Mid-West Region (Distrito Federal, DF). Most patients were 50–69 years old, and only three were between 30 and 49 years old. Among the interviewed patients, only two of them were diagnosed with metastatic breast cancer. Only two of the interviewed patients were diagnosed with metastatic breast cancer. Fifty-three women from all five Brazilian regions answered the online questionnaire applied in October and November 2020. These breast cancer patients were between 30 and 69 years old and eleven were diagnosed with metastatic breast cancer. Most participants were diagnosed with BC diagnosis between 2018 and 2020, i.e., in the last two years (Table 1).

Interviews

Tamoxifen was the most widely used breast cancer medication among study participants ($n = 8$). One of the patients reported that, due to side effects, she recently had to stop taking anastrozole, and is currently taking only tamoxifen (Table 1).

The most reported side effect related to breast cancer treatment was fatigue ($n = 11$) and hair loss ($n = 10$) (Figure 1). Other side effects such as loss of appetite, heartburn, dyspnea, osteopenia, difficulty concentrating, general dryness and peripheral neuropathy were also reported during the interview.

Psychological and emotional impact were frequently described, even though we didn't specifically mention these aspects in the interview (we've given as examples physical, sexual, social, and economic aspects). Some of the patients used similar sentences to narrate the difficult moment of the diagnosis, as seen below.

> "It was such a surprise because I used to take care of myself, I always had healthy habits" (MCTR, 56 years old, BC)

> "It was a huge surprise… I didn't have any node, nothing. It was discovered during the annual checkup and I was in shock. Despite we know there's a treatment, you feel too afraid of the future (TS, 56 years old, BC)

> "My life was totally affected. My life was very different before cancer. When I was diagnosed, I got deeply depressed, I was sure I was going to die. It was an enormous suffering" (TMLPRA, 61 years old, BC)

> "I feel much more fragile after the diagnosis and with this treatment, I cry frequently… I feel like a baby" (PEBB, 45 years old, metastatic BC)

Mental health was described as something important during the treatment and it seems integrative practices - such as natural foods, meditation, yoga - have importance on this aspect for some of the interviewed oncological patients, as we can see in the following quotes:

TABLE 1 Characteristics of the participants.

		Number of participants % (*n*)	
		Interview (*n* = 12)	Survey (*n* = 53)
Age			
	<30	0	0
	30–49	25 (3)	49 (26)
	50–69	75 (9)	47 (25)
	>70	0	0
	NI	0	4 (2)
City/State			
Southeast Region	Rio de Janeiro, RJ	60 (7)	24 (13)
	Duque de Caxias, RJ	8 (1)	0
	São Paulo, SP	8 (1)	5 (9)
	Contagem, MG	8 (1)	0
	Aparecida, SP	0	2 (1)
	Hortolândia, SP	0	2 (1)
	Itu, SP	0	2 (1)
	Praia Grande, SP	0	2 (1)
	Santo André, SP	0	2 (1)
	Santos, SP	0	6 (3)
	Belo Horizonte, MG	8 (1)	4 (2)
Mid-West Region	Brasília, DF	8 (1)	15 (8)
South Region	Morretes, PR	0	2 (2)
	Florianópolis, SC	0	2 (1)
North Region	Belém, PA	0	4 (2)
Northeast Region	Fortaleza, CE	0	22 (12)
	Caucaia, CE	0	2 (1)
Diagnostic			
	BC	83 (10)	79 (42)
	Metastatic BC	17 (2)	21 (11)
Current drug treatment			
	Tamoxifen	67 (8)	30 (19)
	Anastrozole	17 (2)	13 (8)
	Letrozole	17 (2)	8 (5)
	Pembrulizumab	0	0.5 (1)
	Pabociclib	8 (1)	0.5 (1)
	Pertuzumab	8 (1)	3 (2)
	Trastuzumab	8 (1)	5 (3)
	Goserelin acetate	17 (2)	5 (3)
	Zoledronic acid	0	5 (3)
	Chemotherapy	0	3 (2)
	Exemestane	0	5 (3)
	Does not take any drug	17 (2)	22 (14)
Time since first BC diagnosis			
	< 2 years (2018–2020)	NA	45 (24)
	2–4 years (2016–2017)	NA	28 (15)
	4–6 years (2014–2015)	NA	6 (3)
	6–8 years (2013–2012)	NA	9 (5)
	>8 years (<2011)	NA	8 (4)
	NI	NA	4 (2)

BC, breast cancer; NA, not applicable; NI, not informed; RJ, Rio de Janeiro; SP, São Paulo; MG, Minas Gerais; DF, Distrito Federal; PR, Paraná; SC, Santa Catarina; PA, Pará; CE, Ceará.

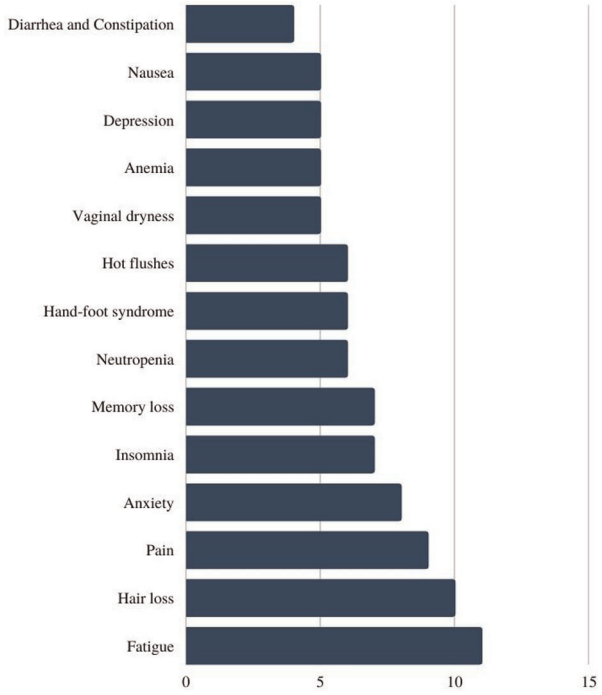

FIGURE 1
Most reported side effects related to breast cancer treatment (absolute numbers).

> "I found the Zen Cancer Institute and I could stop 1 year to take care of myself, look at my mental health, self-knowledge, meditate, integrative practices like yoga. I allowed myself to do things that are good for me, that brings me positivity. That was the greatest positive impact: a better mental health" (RMBL, 44 years old, BC)

> "I"m pretty sure 50% of my results were due to the integrative medicine associated with the traditional treatment" (LVSG, 61 years old, BC)

Impact on self-esteem was also reported and it was frequently related to the loss of hair and to the mastectomy. Many patients continue to undergo psychotherapeutic follow-up since the breast cancer diagnostic.

> "I never worried about appearance and then, I started to change it, to go out on the streets and even at home with my family. My husband"s support was fundamental for my self-esteem maintenance" (MCTR, 56 years old, BC)

> "Cancer affected everything, in terms of life expectance, quality of life, sexually speaking, my self-esteem… I had depression and I"m still treating it with a psychiatrist" (DSG, 44 years old, BC)

When asked about what aspects of life were more affected, all patients mentioned that the disease had a strong physical impact, mainly related to consequences of the chemotherapy and surgery (mastectomy and axillary lymph node dissection). Pain, limiting fatigue, appearance changes – due to loss of weight, hair and breasts, loss of strength, and balance limiting exercise routine were some of the described physical impacts.

> "The physical aspect, because I didn"t do the breast reconstruction surgery, so to look at me in the mirror, my sexuality, my relationship with my husband are aspects that are getting better little by letter. Tamoxifen induced my menopause. I still can"t do exercise; I don"t have good mobility on my left arm because they extracted 4 lymph nodes" (DSG, 44 years old, BC)

> "I wake up feeling pain, I have gastric reflux and other gastric adverse effects because of the many medicines I take" (PEBB, 45 years old, metastatic BC)

Six patients related negative impacts on sexual life. Vaginal dryness and loss of libido were frequently reported as the cause but a strike on self-esteem and emotions was also reported as possible reasons to affect this aspect.

> "My libido decreased a lot during chemotherapy. But my husband respected this moment, supported and understood me. It was getting better after the chemo and surgery" (MRAS, 56 years old, BC)

> "It"s so complicated, depressing. There is vaginal dryness, atrophy, there is no libido, the act hurts, it becomes mechanical, it is no longer pleasant. It was the most affected part" (PEBB, 45 years old, metastatic BC)

According to most of the interviewed patients, the impact on social life was surprisingly positive. Many women reported that, despite they have found some stigma coming from society, they had an improvement in social life, mainly when there was a strong support network like family, close friends and Cancer Support Non-Governmental Organizations. However, some patients described uncomfortable feelings due to the lack of knowledge about the disease. On one hand, some people approached them like cancer was a death sentence or, on the other hand, others didn't understand how the patient was sick if they were apparently doing so great. The importance of cancer awareness, besides better access, was cited as an important action that should be established by health authorities.

> "Social aspects were positively affected because to deal with other people got easier for me. Since I had to go through all this suffering, I am more empathetic. Things that used to annoy me, don"t bother me anymore. I feel more like a conciliator between people nowadays" (AFS, 52 years old, BC)

> "Socially, I felt a lot of support from friends, I was not isolated nor marginalized, I felt welcomed. There were some restrictions, the surgery was in the summer, so I became more secluded, quieter, but it is not difficult to live with herself (…) There were people visiting. At work, I didn't feel any prejudice. Although there is still a stigma, people are terrified, scared. It was difficult to deal with a diagnosis that nobody wants to have" (ACF, 53 years old, BC)

> "The social aspects were very affected. With close people, I didn"t have any problem, I have friends and family supporting me. But I had difficulty with other people, mainly after I cut my hair before losing it completely, they noticed I had something. Most people didn"t know at work, so it was hard to deal with it" (MCTR, 56 years old, BC)

> "Someone asked, "You have cancer, are you going to die?" and I replied, "I'm going, aren't you?" Cancer is not punishment, I do not see it as punishment, but as a school, a great learning experience, I am a better person than I was before." (JG, 58 years old, Metastatic BC)

Half of the interviewed patients ($n = 6$) reported breast cancer brought an economic impact on their lives, mainly for patients that rely on public health system or those who were unemployed or had to stop working because of the disease or its treatment. But even patients who have health insurance reported impact due to the need for expending more money on healthier food, medicines, exams, and doctors which were not covered. All patients that mentioned not having an economic impact had health insurance.

> "Economically affected me a lot, mainly in the beginning, because I had to get a medical leave and my salary was lower and I had a lot of expenses with medicines that my health insurance didn"t cover. But after I retired from one of my jobs, things got better" (AFS, 52 years old, BC)

> "I used to work but now I"m retired because of the disease. I spent a lot of money on physiotherapy and medicines. I do not have health insurance, my treatment is under SUS, but some medicines are not available, they are costly, and we have to buy it" (DSG, 44 years old, BC)

The exam routine was another frequently mentioned stress factor. The fear of another diagnosis was present in most analyzed discourses.

> "When we have a diagnostic like this, you live with fear all the time, because it"s something that you would never imagine happening in your life… it comes from nowhere and it can always come back" (TMLPRA, 61 years old, BC)

> "Every year I do mammography and I get so scared; I don"t want to go through everything again. We"re always scared, every year I go to do mammography I get scared and nervous" (RP, 68 years old, BC)

> "I"m terrified of having a recurrence. I have depression and anxiety, so something that affects me a lot is this fear of having cancer again" (LVSG, 61 years old, BC)

Online questionnaire

When inquired to report how they would evaluate their health state in the last seven days most participants declared "excellent" health state ($n = 27$, 51%), followed by "good" ($n = 19$, 36%), "moderate" ($n = 4$, 7%) and "bad" ($n = 3$, 6%) (Figure 2). Similar results were observed when the patients were inquired to report how would they evaluate their quality of life in the last seven days. Most women self-reported "excellent" quality of life ($n = 25$), followed by "good" ($n = 22$), "moderate" ($n = 3$), and "bad" ($n = 2$) and "very bad" ($n = 1$) (Figure 3).

When asked about their current drug treatment, seven patients declared having two or more associated oral medicines as part of their current treatment. Most of the patients that answered this survey ($n = 19$) reported tamoxifen as part of their current oral therapy, followed by patients who were not taking any medicine ($n = 14$) and patients taking anastrozole ($n = 8$) — in association with other drugs or not. Both patients that reported being under chemotherapy were diagnosed with metastatic breast cancer at the time of this survey (Figure 4). As for the duration of use of the drugs mentioned above, twenty-five women reported their use for more than ten months.

The treatment effects that were less and the least important were adverse events ($n = 23$) and pain ($n = 25$), respectively (Figure 5). Here, it's important to consider the main profile of these patients, mostly breast cancer patients without metastatic disease. The increase of the overall survival was

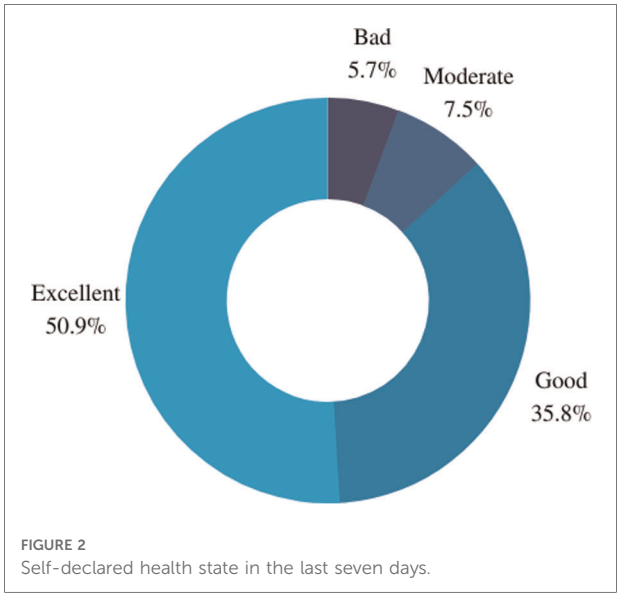

FIGURE 2
Self-declared health state in the last seven days.

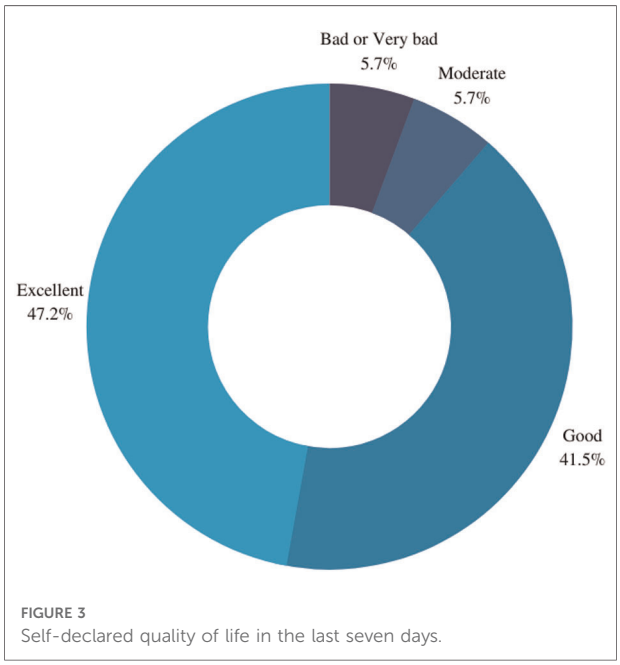

FIGURE 3
Self-declared quality of life in the last seven days.

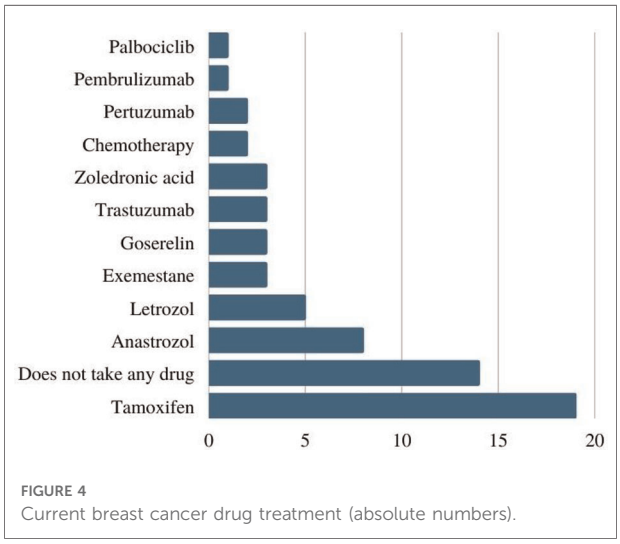

FIGURE 4
Current breast cancer drug treatment (absolute numbers).

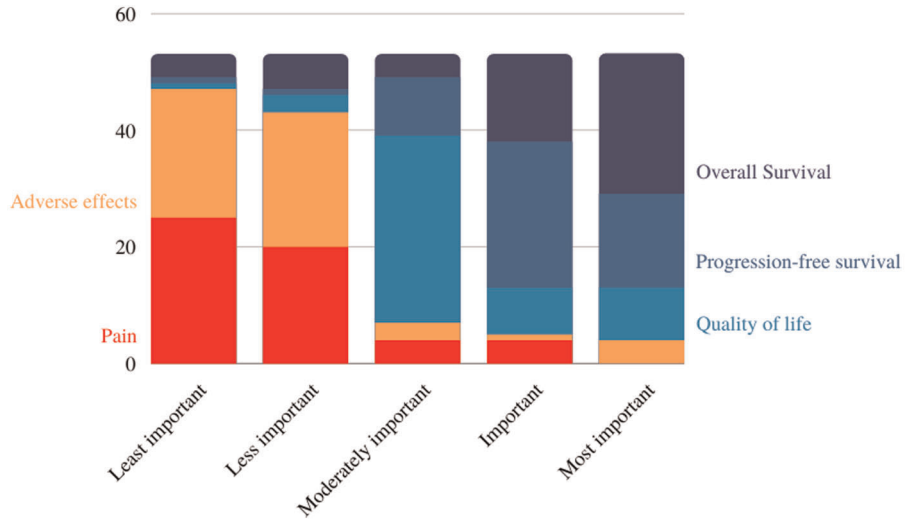

FIGURE 5
Treatment outcome ranking (absolute numbers).

considered the most important ($n = 24$) and progression-free survival was considered an important effect ($n = 25$).

When asked "what is your main treatment objective?", most women considered cure ($n = 39$), progression-free survival ($n = 7$) and quality of life ($n = 5$) as the main goals of their treatment - even if they were diagnosed with metastatic disease. When faced with the possibility of cure, overall survival increase ($n = 1$) ranked behind quality of life. One patient who was under chemotherapy treatment mentioned "to reduce tumor size" as her main treatment objective (Figure 6).

The replies to the surveys revealed that, when asked to choose the aspects of life that breast cancer had the greatest impact on, the psychological and emotional component represented the most important ($n = 29$). The economic aspect was considered important ($n = 15$) by the Brazilian patients, followed by the sexual aspect, considered moderately important ($n = 15$). Social aspect was considered less important ($n = 19$) and physical aspect was evaluated as the least important ($n = 18$) (Figure 7).

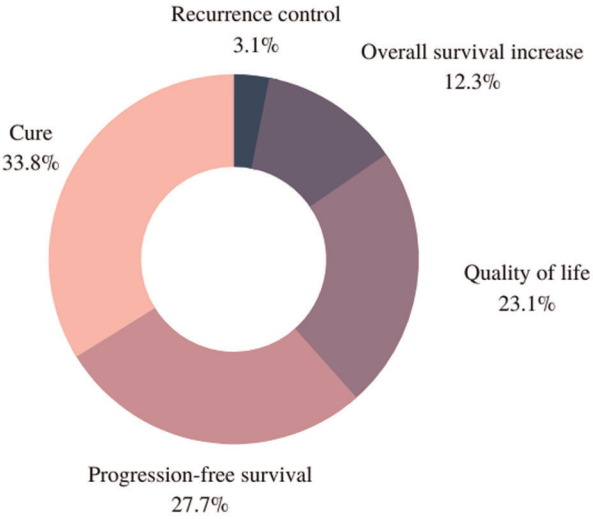

FIGURE 6
The main treatment objective.

Discussion

As far as we know, this is the first study that sought to understand the most important outcomes for breast cancer patients in Brazil. Typically, studies focus almost exclusively on clinical outcomes, that is, they focus only on what researchers consider important. In this study, we found that clinical outcomes such as cure, overall survival, survival free of progression (which Brazilian patients call "controle da doença", translated as progression-free survival), and quality of life are important for Brazilian patients, but so are other secondary outcomes that showed large impact on these women's lives. For example, for patients who responded to the online questionnaire, the condition itself and its treatment have a great psychological and emotional impact, an aspect considered as the most important when compared to physical outcomes or social, sexual and economic impact. The sexual aspect was found as moderately important, and is related to frequently reported adverse effects, such as decreased self-

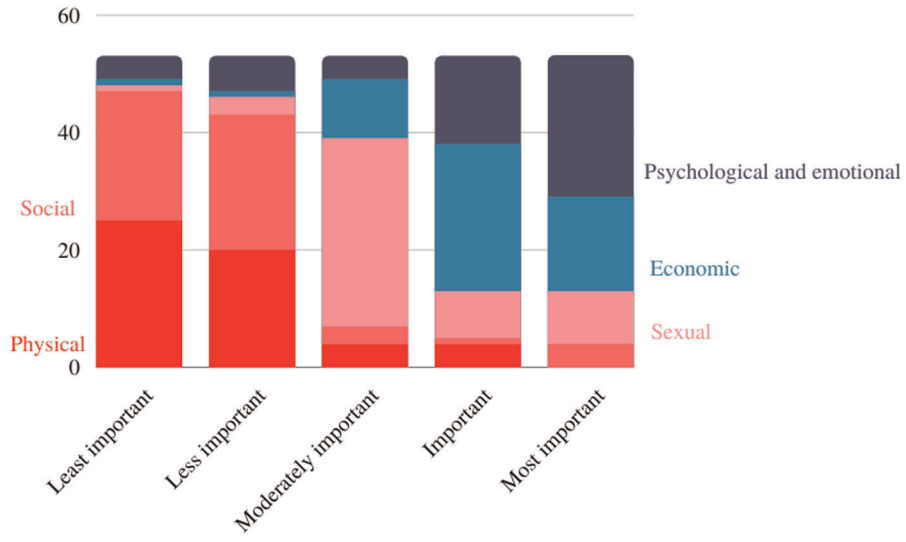

FIGURE 7
The most impacted aspects of life.

esteem and libido, vaginal dryness, but may also be related to the emotional impact of the disease on these patients lives.

According to our findings, overall survival and progression-free survival are the most important treatment outcomes, showing that our findings are aligned with a recent survey that sought to rank the most valued outcomes for cancer patients (22). Despite this, some authors question the relevance of this outcome. However, recent research revealed that patients who remain in the PFS state might postpone chemotherapy. Also, using of PFS results is essential to support other outcomes in economic analyses regarding breast cancer treatment (23).

It is noteworthy to highlight that the women interviewed frequently reported the condition and its treatment as having a significant physical impact. Adverse events such as pain and fatigue have often been described. However, when analyzing the sample of women who answered the online questionnaire, the physical aspect was described as the least important, when compared to other aspects. For these patients, cure or an overall survival were the most expected treatment results, followed by progression-free survival and quality of life. The treatment effects considered less important were adverse events and pain was showed as the least important effect. Here, it is important to consider the main profile of this sample, formed mainly by patients with breast cancer without metastatic disease. Of a total of 65 women who participated in this study (through both interviews and online questionnaires), only thirteen were diagnosed with metastatic cancer.

A limitation of this study is the small sample of participants, mainly when compared to the total population of Brazilian women with breast cancer. The estimation for the triennium of 2020 to 2022 was 662,80 new cases in Brazil (24). Therefore, we understand this is not a representative sample. Another limitation is the fact that the data collection instrument used was not a validated questionnaire. Due to the short time, the research team decided to apply a questionnaire that could be feasible, in addition to reflecting the perspective of Brazilian women regarding the disease and its treatment in relation to the ethical, social impacts, and other results reported by the patient. It is noticed that the instrument built and used could capture some issues that generic instruments cannot, due to the lack of sensitivity. Some of the important aspects and results captured by this research are not addressed in most generic instruments, as is the case with SF-6 or EQ-5D.

In this sense, the importance that health-related quality of life has for women diagnosed with breast carcinoma is evident. However, this outcome is often overlooked in clinical studies of different cancer treatment options, in which priority is given to overall survival, for example (25). To propose improvements in the sensitivity of instruments to capture issues related to the quality of life, they must be specified to effectively encompass patient preferences in the context of incorporating technologies, through the integration of experience of patients in the work processes of the different HTA agencies.

Despite all the negative impacts addressed, the benefit that integrative practices provided for the cancer patients interviewed is notorious, when it comes to mental health and good prognosis. Traditionally, researchers tend to focus on the negative consequences of cancer, however going beyond this

one-sided view and studying the positive aspects also promote improvements in the line of care. This finding corresponds to the process of personal development and can be called post-traumatic growth, taking into account that breast cancer is a psychosocial process and includes positive and negative consequences for the individual (26).

The present study highlighted the perspectives of patients diagnosed with breast carcinoma regarding the challenges of the disease and their preferences about the lines of treatment. Given the relevance of the presented findings and the scarcity of studies that reflect this scenario, it is necessary to explore the experiences of women in this context, to ensure improvements in the process of health technologies assessment are patient-centered, encompassing the cultural and socioeconomic aspects of the different contexts and countries.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary materials, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Instituto Nacional de Cardiologia. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ASS and ACWF contributed to the data collection, conception, design, analysis, and interpretation of data and the writing of the paper (ICMJE rules) and have approved the submitted version. MSS, CASM, MPP, LSM contributed to the interpretation of data, writing of the paper, and have approved the submitted version. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Engaging patients and citizens in digital health technology development through the virtual space

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Digital technologies are increasingly empowering individuals to take charge of their health and improve their well-being. However, there are disparities in access related to demographic, economic, and sociocultural factors that result in exclusion from the use of digital technologies for different groups of the population. The development of digital technology in health is a powerful lever for improving care and services, but also brings risks for certain users in vulnerable situations. Increased digital health inequalities are associated with limited digital literacy, lack of interest, and low levels of self-efficacy in using technology. In the context of the COVID-19 pandemic and post-pandemic healthcare systems, the leap to digital is essential. To foster responsible innovation and optimal use of digital health by all, including vulnerable groups, we propose that patient and citizen engagement must be an essential component of the research strategy. Patient partners will define expectations and establish research priorities using their experiential knowledge, while benefiting from rich exposure to the research process to increase their self-efficacy and digital literacy. We will support this proposition with an operationalised example aiming to implement a Virtual Community of Patients and Citizens Partners (COMVIP), a digital tool co-created with patients and public experts, as active team members in research. Founded on the principles of equity, diversity and inclusion, this base of citizen expertise will assemble individuals from different backgrounds and literacy levels living in vulnerable situations to acquire knowledge, and share their experiences, while contributing actively in the co-development of innovative strategies and health technology assessment.

KEYWORDS

digital health, patient and citizen engagement, underrepresented groups, virtual collaboration, co-development.

Introduction

Digital tools have developed rapidly over the past two decades and are being used increasingly in healthcare as they are associated with improved well-being and health (1, 2). They facilitate clinician-patient collaboration and encourage patients to interact and participate actively in their care. Furthermore, the active involvement of patients

in their care process allows for improved clinical outcomes and health services quality (3, 4). The use of digital tools in healthcare is essentially changing the way clinicians deliver care and inform patients about their health (3, 4). Digital tools have the ability to easily adapt to change and to people's profiles because of their versatility and dynamism (3). However, social inequalities cause significant disparities in access to Canadian health services and digital technologies (5–10). Vulnerable populations are often underserved by telecommunications services and are deprived of optimal access to employment, education and health and social services (5–9). They are more prone to chronic diseases, social isolation, lower socio-economic status, lower education and harmful health behaviours such as smoking (8–11). Digital technologies help break isolation of older people living alone, however their use is often hindered by a lack of access and familiarity with their use (7, 8). Cultural minorities, including Indigenous populations, are underrepresented in digital heath data, which causes biases against them when using these tools (12). They also have difficulty searching for, and understanding health information and services using digital tools (8, 9).

The COVID-19 pandemic accelerated use and adoption of digital health technologies, while showing the ability of digital solutions to meet many of the population needs (4). However, the access and use of digital health innovations by specific population groups in vulnerable situations remain limited. These digital health inequities may be associated with a range of factors. Among others, certain demographic, economic, and sociocultural characteristics, limited computer literacy, lack of interest, and low levels of technology self-efficacy are barriers to digital health tools (4, 13). In addition, digital health technology solutions are proving inadequate to meet the specific needs of vulnerable groups as they are often designed without their insight and experiences (14, 15). People typically underrepresented in digital health solutions include, older adults, people living with disabilities, youth in difficulty, people from cultural minorities, and Indigenous people (**Figure 1**).

Underrepresented groups do not fully benefit from the opportunities offered by digital technologies to access health services (13). This article presents the concept of patient and public engagement in the development of a digital health technology platform and an example of its application using an innovative co-creation methodology.

Patient engagement towards digital technologies

Meaningful patients and citizens' engagement in the research process is of utmost importance for successful implementation and application of research results (16). To achieve the goal of active patient and public engagement, it is imperative to foster an inclusive climate in which all those involved in the research process understand the value of shared experiential knowledge and (16). Patients and public partners can take meaningful and key roles in research by supporting access to peer networks and difficult to reach groups and peer-to-peer recruitment (16). This can also apply to the development of useful and adaptable digital technology intended for patients. To increase the adoption of digital tools, it becomes essential to enhance and encourage users' engagement as active participants in technologies co-creation. Meaningful engagement leads to an improved understanding of their experiences, preferences, needs, as well as potential limitations of digital tools (13, 14, 17).

For a digital technology to be useful and effective, it requires for its features to have the potential to attract, adapt and actively immerse the user in its content (18, 19). However, several studies show that the effectiveness of technology interventions may be limited by inappropriate use by the intended users,

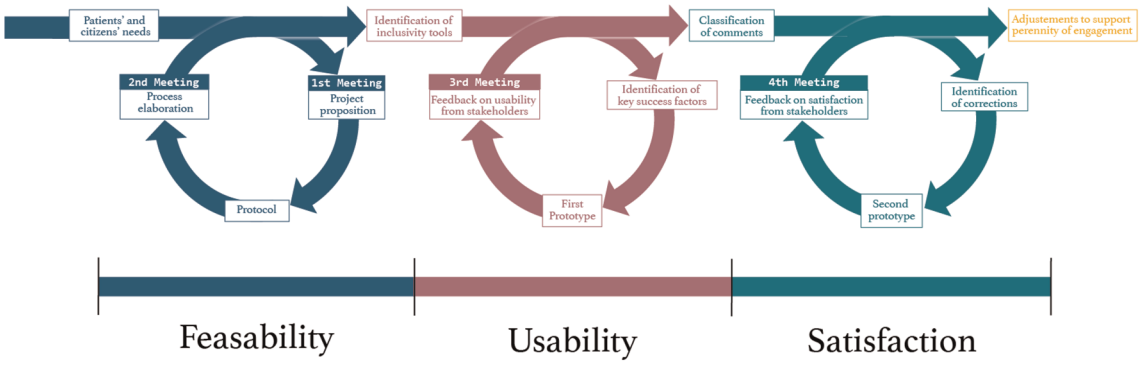

FIGURE 1
The COMVIP project Co-creation process.

leading to the abandonment or rejection of the tool over time (19, 20). Technology design, appearance, and functionality are thus important precursors to user engagement (21). These factors encourage an affective and behavioral connection to the proposed tool (22). Despite the lack of academic consensus, user engagement in health appears to be a multidimensional construct including cognitive, behavioral and affective components that allow the user to effectively adopt a digital tool (21, 22).

Despite the growing presence of tools to evaluate engagement, the use of inclusive approaches from a variety of fields is still needed to allow their application to diverse groups (23). These tools should combine both quantitative and qualitative assessment of users' perspectives in the design and use of technologies (23–25). As such, the design process of The Virtual Community of Patients and Citizens Partners (COMVIP) strived to integrate patients and users' perspectives, from the conception of the research process to the development and testing of the platform to ensure maximum retention, adaptability and satisfaction.

The digital tool created will allow for its continuous design evolution and options' adaptation according to user experience and patients and public preferences, therefore, maintaining engagement over time. By monitoring patients and public usage activity within the platform and openly discussing barriers and needs, COMVIP may adapt more effectively to users. As such, it allows for the continuity and sustainability of research projects and digital technology development, which are quality indicators of engagement (26). Thus, COMVIP seeks to adjust to the current and future needs of its intended users by presenting an adaptable, customizable, informative and inclusive navigation environment.

Answering a collective need: the virtual community of patients and citizens (COMVIP)

To support the efforts towards patient and public participation in the development of digital technologies in research and health technology assessment, the idea of a virtual platform for knowledge and experience sharing was born. This feasibility project aims to implement and evaluate COMVIP, an innovative intervention co-constructed by patient and citizen partners, researchers and community organizations. It is founded on deliberative approaches (27) and Canadian Institutes for Health Research (CIHR) Patient Engagement Framework's principles of equity, diversity, support, mutual respect, co-building and inclusion (16). A partnership with patients and citizens has been established for the co-creation process depicted in this article. The team can count on the active involvement of patients and citizens as they are considered members of the research team and collaborate in each step of the research project. Their active involvement will provide support through shared experiences in care and use of technology. Patients and citizens are considered experts in the different research methods and activities, and will participate in the writing of the research protocols, planning of research methods and implementation and dissemination of the research results. COMVIP will provide an opportunity to gain knowledge, share experiences, and support team members in the process of digital ownership and empowerment.

The objectives of this project were to:

(1) foster meaningful engagement of patients and citizens in the development of digital technologies in health;
(2) increase digital health literacy and level of confidence in the use of health technologies;
(3) identify barriers of effective digital health tools use.

The project will contribute to the digital transformation in health and health technology assessment by involving users in tools development. It will promote strategies aimed at under-represented groups inclusion in digital health projects in Canada and elsewhere in the world and will guide practice implementation to encourage user empowerment. Digital technologies can be seen as a lever for rapid access to care and services and better resource utilization. The inclusion of end users in the design of digital health projects favors adoption of digital tools and it is a recognized approach for a responsible innovation process (2, 28). Patient and citizen partners will be invited to define their expectations and establish their priorities in the use of digital solutions that will then be co-developed and tested in subsequent research projects.

Patients and citizen partners come from a variety of backgrounds (community organizations, Indigenous peoples, immigrants, people living with specific health conditions) and are committed to the development of COMVIP. To them, this platform is a lever for making their voices heard and influencing the digital transformation of the healthcare system. For the team members who come from the domains of academic research and the development of digital solutions, COMVIP responds to a need for access to the experiential knowledge of people who could benefit from the use of digital tools in health, but who often remain difficult to reach.

The project inspired the creation of an innovative and iterative methodology adapted to the existing circumstances associated with COVID-19 that limited physical interactions. This co-construction model allowed team members to cooperate effectively and begin the COMVIP platform design process in a virtual setting.

An innovative and iterative methodology: A co-creation process

The research team is composed of university professors, health professionals, graduate students and experts in the fields of medicine, nursing, public health, social sciences, education, ethics, marketing, mathematics, computer science and AI from different institutions in the Province of Quebec such as Université Laval, the Université du Québec à Montréal (UQAM), the Université de Montréal, the Université du Québec à Trois-Rivières and the Centre de recherche universitaire sur les jeunes et les familles (CRUJeF). The research team also counts on the active involvement of expert patients and partners from the Unité de soutien système de santé apprenant Québec and community organizations such as the Centre d'amitié autochtone du Québec, the Association des étudiantes et étudiants de l'Université du 3e âge de Québec (AEUTAQ), the Regroupement des organismes de personnes handicapées de la région de la Capitale-National ROP03) and the Service de Référence en Périnatalité pour les Femmes Immigrantes de Québec, among others.

We opted to use a collaborative application and conferencing tool to work remotely on the same documents, allowing sharing real time advancement in the project with all involved. A first virtual meeting took place on February 2021 to officially launch the COMVIP project. The senior researcher of the project ascertained beforehand the ability of all team members to access a virtual meeting and interact efficiently. Since sanitary measures were implemented in March 2020, attendees were comfortable with virtual gatherings. They were considered increasingly useful for social engagements (work meetings, webinars, concerts, family meetings, public hearings, etc.).

As noted by Rasburn and colleagues (29), there are numerous benefits to having virtual meetings as a working tool. It enhances accessibility, by removing barriers that could have prevented participation; inclusivity, by allowing participants to control and adapt freely the conference tool's settings (lighting, speaker sound, microphone sound, camera) and feel comforted by being in their own environment; and transparency, by allowing more people to attend and observe gatherings (28). Virtual meetings enable participants to attend team gatherings from home thus, reducing travel time, costs, fatigue and recovery time (29). Moreover, they are easily accessible for people who live further from the physical location of the meeting, who have caring responsibilities, work engagements or other commitments (28). Consequently, it enables the research team to invite more people and have a broader range of perspectives (28). The research team adapted to digital literacy levels by actively listening to attendees' problems and making themselves available to solve any technical difficulties before officially starting the gatherings.

A co-creation process was implemented to ensure that patients and citizens' perspectives would be fully integrated in the platform development, since it is destined to be used by them and to benefit their associated population. An inclusive approach to co-creation and co-production enhance patients and public engagement in projects in line with their priorities and interests, and facilitates the implementation process (30, 31). The research team made a great effort to ensure and stimulate the collaboration and participation of everyone in the discussion, encourage them to share their personal knowledge, consider others' opinions and use group tensions to enhance creativity and productivity (32, 33). This allowed all members to express themselves in a respectful and inclusive environment that favors successful patient engagement (26). In a co-creation process, it is suggested that stakeholders go through an iterative process (34). Thus, the research project adhered to a cycle of co-creation consisting of four steps: exploration of solutions and avenues; decision-making about what ideas should be kept; creation of a prototype and evaluation of the prototype (34).

Patients and other stakeholders came mostly from Quebec City and Montreal and were involved in the conception of COMVIP from the beginning. During the first meeting, which took place on February 8, 2021, the research team discussed about the objectives of the research project and the platform's intent, so that all involved agreed upon the aims and develop a shared purpose which is a key patient engagement quality criterion (26). Then, team members could comment, discuss limits and barriers from their perspective and propose opportunities and ideas to the research team. All team subgroups were present and represented by at least one member during the gathering (patient and citizen partners, community organization representatives, researchers working on patient-centered care projects and team members leading the project) to reach stakeholders' representativeness (26). The first meeting allowed to explore the feasibility of the COMVIP platform with intended users and stakeholders. During the second team meeting, which took place on April 20, 2021, participants identified together content and functionalities to be added to the prototype according to users' identified needs. From April 2021 to May 2022, the research team developed a platform prototype with the help of a graphic designer and web developer. The prototype creation was inspired by Ruel and Allaire's guide on accessible information (35) and the Web Content Accessibility Guidelines (WCAG) international standard for people with disabilities from the W3C Web Accessibility Initiative (36). The result of the co-creation process was the development of a single-paged and easy-to-use platform prototype. It offers simplified menus for rapid and easy access to specific content (e.g.,: forums, courses, profile), font size modification icons for better reading experience, vivid colors adapted to the visually impaired and color-blind, inclusive images representing the variety of peoples and cultures that make up the population, easy access to projects' description and a space presenting the name, photo and contact information of the different members of the COMVIP team.

FIGURE 2
A portrait of Canadian underrepresented groups living in vulnerable situations.
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The COMVIP prototype was presented to stakeholders during a third team meeting which took place on May 12th, 2022. The leading researchers invited everyone to comment, give their opinion, and propose possible improvements. The prototype was positively welcomed by patients and citizens partners and researchers. New comments and propositions for better user experience and easier navigation were gathered from their feedback, such as the development of user stories, the inclusion of an introductory user descriptive video clip, standardized project profile resumes and the addition of useful project links. Thus far, three meetings have taken place either online or in hybrid mode and lasted two hours each. An average of twenty people attended each meeting and every subgroup was represented by at least one person or more. All team members from professorial and experts in the different fields previously mentioned were present during the meetings.

All the different opinions and propositions will be reviewed according to two criteria: significance and feasibility. This process will guide decision choices about which propositions to be added to the platform. The feedback obtained from the meeting helped understand the usability of the platform and the need for minor corrections and additions. Finally, the research team will conduct an improvement iteration of the platform according to feedback. A fourth meeting will be organized in order to present the final version of the COMVIP platform and present the changes made to team members in order to evaluate their satisfaction. By the end of the project, the group should have come through three steps of the cycle of co-creation: feasibility, usability and satisfaction of stakeholders (**Figure 2**).

Discussion

Through online workshops and showcases, people from various backgrounds can engage in the co-development of digital health solutions adapted to their needs. According to CIHR Patient Engagement Framework (16), successful patient engagement incorporates inclusive mechanisms and processes that allow patient and public involvement at all levels of the research process, a multi-way capacity building that promotes the development of stakeholders' capacities and a safe environment for open interactions and effective teamwork, a multi-way collaboration and communication by fostering mutual respect, an experiential knowledge of stakeholders that is valued as evidence and translated, collaborative methods of research that are inclusive and recognizes a diversity of patients, and a shared sense of purpose that allows stakeholders to work together towards a common and stay informed about research outcomes. Guided by this framework, we can concede that COMVIP supports patient and public engagement successfully in its research methods and co-creation design process. This project effectively empowers and includes stakeholders through every research and development stage while valuing stakeholders' key role through shared personal experiences and appreciation.

The participants engagement towards COMVIP will be key to its successful adoption, implementation and sustained use by stakeholders and public.

Once officially launched, COMVIP will help develop knowledge about the needs and challenges of vulnerable groups with respect to their acceptability of digital technology, beyond technical considerations, and about the factors that can promote digital health literacy among these groups. In addition, this project will help develop knowledge on the conditions that promote the commitment and continued involvement of patients and citizen partners in this type of research, as well as on the impact of their involvement in the development of digital solutions in health and social services.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Comité d'éthique de la recherche du Centre intégré universitaire de santé et de services sociaux (CIUSSS) de la Capitale-Nationale. The patients/participants provided their written informed consent to participate in this study.

Author contributions

RHBS drafted the article's manuscript, L-AB-D participated in the draft and developed all of the articles images. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Civil society and medical product access in Africa: Lessons from COVID-19

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Understanding health as a human right creates a legal obligation on countries to ensure access to timely, acceptable, and affordable health care. We highlight the importance of a meaningful role for civil society in improving access to well-regulated quality medical products in Africa; to support and be part of a regional social contract approach following the access issues that have been particularly evident during the COVID-19 pandemic. We argue that African communities have a clear participatory role as important stakeholders in the regulatory lifecycle. Solidarity is important for a cohesive approach as formal government healthcare infrastructure may be minimal for some countries, with little training of communities available for disease management and insufficient money to fund people to organise and deliver health care. Some of the issues for civil society engagement with multi-stakeholders, and possible mitigating strategies, are tabulated to initiate discussion on facilitators and concerns of governments and other stakeholders for meaningful participation by patients, communities and civil society within a regional regulatory lifecycle approach. Solidarity is called for to address issues of equity, ethics and morality, stigmatisation and mutual empowerment – to sustainably support the region and national governments to develop greater self-sufficiency throughout the regulatory lifecycle. By creating a participatory space, patients, communities and civil society can be invited in with clear missions and supported by well-defined guidance to create a true sense of solidarity and social cohesion. Strong leadership coupled with the political will to share responsibilities in all aspects of this work is key.

KEYWORDS

civil society engagement and participation, regulatory lifecycle and value assessment, human rights, social cohesion, low and middle-income African countries

Definition

Civil society: Communities and groups that work outside of government or commercial bodies. The sector of society distinct from government and business, and including the family and home.

Introduction

Understanding health as a human right creates a legal obligation on countries to ensure access to timely, acceptable, and affordable health care of appropriate quality. This is in addition to providing for the underlying determinants of health such as safe and potable

water, sanitation, food, housing, health-related information and education, and gender equality (1). A rights-based approach to health requires that health policy and programmes must prioritise the needs of those furthest behind first, towards greater equity, without discrimination on the grounds of race, age, ethnicity or any other status. Another important feature of rights-based approaches is active participation. That national stakeholders are meaningfully involved in all phases of assessment, analysis, planning, implementation, monitoring and evaluation. This includes community and non-state stakeholders such as non-governmental and civil society organisations (1, 2). Community and patient experiences, burdens of disease, patient needs and issues of equity and stigma are important considerations in health care (3), where value assessments are influenced by social and historical settings (4). Some countries may however lack political freedom or will to transparently discuss and define their priorities in building the required resources to deliver on health care.

An existing model

The United States. President's Emergency Plan for AIDS Relief (PEPFAR) is an example of a United States. government's global effort to change the trajectory of the global HIV epidemic. This program has sought to move to a model of country ownership (governments and organisations), not just local non-government organisations (NGOs) (5). Sustainable global health programs therefore ultimately require states to mobilise resources and channel funding to directly manage such programs.

The objectives of the present project are to:

1) highlight the importance of human rights in equitable access to health care and medical products in Africa, and the active participation of patients, communities and civil society in policies and strategies to build effective and cohesive regulation, value assessment and appropriate actions within the regulatory lifecycle;
2) identify some of the challenges to providing quality medical products in Africa;
3) Identify issues for patient, community and civil participation with possible mitigating strategies, to enable meaningful engagement.

Our intention is that through this work we can raise awareness, inform discussions, trigger actions and promote further study. An empirical review of the current literature was applied to inform the project. We also searched selected grey literature sources, collated sources already known to the authors and put out requests to our networks (including through social media). When we identified papers, we checked the references of those papers.

Access to quality medical products in Africa – the developing situation

The world's experience of the COVID-19 pandemic has made it clear that Africa as a region cannot solely rely on charity from higher income countries to provide essential health care to meet therapeutic needs in line with International Human Rights (6–8). African countries need to work together within a social contract model (9) to build relevant healthcare infrastructure, capacity and medical supplies for the health security of their individual populations. The region needs to strengthen its own pharmaceutical industry to manufacture vaccines and other essential medical products to improve supply and access (10).

The existing Africa Centres for Disease Control and Prevention (CDC), and its regional collaborating centres, was officially launched in January 2017 and is a public health agency of the African Union (AU). It was set up to support the public health initiatives of member states by strengthening capacity and capability of Africa's public health institutions based on data-driven interventions and programmes (11). Overall, it is recognised that the region would be well-served by coordinating and collaborating its efforts, communicating clear missions, guidance and evaluation strategies, and demonstrating solidarity between countries to increase negotiation power and access to medical products. During COVID-19, efforts to obtain the vaccine were hindered by protective intellectual property rights provided through patents on technologies, know-how, manufacturing processes and other trade secrets (12, 13). The AU has worked hard over recent years to initiate the African Medicines Agency (AMA) for regulation and approval of medical products (14). An African Pharmaceutical Technology Foundation has been set up to establish technologies that are important for the manufacture of products (10). The AMA was ratified in November 2021 and its Secretariat is being set up in Rwanda (15, 16) as is that of the Technology Foundation. Low income countries are known to suffer from diseases that attract little investment by the global pharmaceutical industry. Preventative treatments could also be more affordable and their uptake increased, as demonstrated for pre-exposure prophylaxis against HIV in the United States (17). Responsible innovation in health is indeed an issue in high income countries leading to calls for collaborative efforts to clarify and set ethical, economic, social and environmental principles, values and requirements to design, finance, produce, distribute, use or discard socio-technical challenges and possible solutions (18, 19). Worldwide, changes are needed to build sustainable, participatory health systems that meet genuine therapeutic needs.

Identified needs and barriers

Early in the COVID-19 pandemic, it was estimated that the risk of dying from the disease was roughly twice as high for people living in lower-income countries as for those in rich nations. By the end of 2021, 64.1% of people living in high-income countries had received at least one dose of COVID-19 vaccine compared to only 5.4% in low-income countries (20). The marketing and political power of a few global vaccine manufacturers were under the spotlight in a situation that totally neglected health-equity principles (21). Nationalism and hoarding kept technological developments for COVID-19 within high income countries (17, 22). Licensing agreements for the manufacture of vaccines in low and middle income countries (LMIC) could not be reached. Refusal to license and transfer the vaccine technology meant that the World Trade

Organization Trade Related Intellectual Property Rights (TRIPs) perpetuated inequitable access to COVID-19 vaccines (23). Stimulating and rewarding innovation is one of the main purposes of patents, together with data and market exclusivity, and large parts of the world were left unprotected from the pandemic even though this could lead to the rise of new variants. Social cohesiveness and solidarity within populations meant that some countries did relatively well during the early phases of the COVID-19 pandemic, for example Japan, Taiwan, Vietnam (24). This showed that if all individuals are considered fairly and equitably in a socially cohesive system then challenges may be addressed in a rational way. Cohesiveness could also contribute to better monitoring and data collection to inform decision making based on epidemiological data and subsequently rapid and efficient control of epidemics.

Particular needs of African countries for access to safe and effective medical products

Africa has a heterogeneous population made up of different cultures and beliefs (25, 26). Geographic location, weather, transport, and other logistics together with procurement, limited infrastructure and staffing strongly influence access to health care in the region (27, 28). The International Declaration of Human Rights (1) is a primary concern with regard to access to health care and medical products, where civil society and community groups have important roles to play (27, 29). Difficulties with procurement, distribution, and storage, particularly when electrical supply, refrigeration and cold storage are needed, continue to limit access to medical products (27).

An important role of regulatory bodies is to enable processes to determine and ensure the safety, documentation, quality and performance of medical products, including medicines and vaccines, medical devices and technologies. These processes determine that the product is effective when compared with placebo or usual treatment and is safe for marketing and access within a population (30). Involving civil society in decision making can increase the quality of the decisions and ensure that new therapies address the specific needs of local communities (31, 32). Not all African countries have regulatory systems that can effectively manage safe entry of medical products into their countries, or enable their manufacture. A Global Benchmarking Tool (GBT) is used by the World Health Organization (30) to evaluate national regulatory systems. The GBT identifies strengths together with areas for improvement and ways to address gaps. This allows assessment of the overall 'maturity' of the regulatory system with Rwanda and some other African countries (eg Ghana, Nigeria, and Tanzania) reaching targets (30).

By working together at a regional level, the more highly (M3) qualified systems can support other countries in developing effective regulatory processes to control the quality and availability of medical products, by whatever mechanism they enter the region (16). Yet working toward an evidence informed system that is transparent, participatory and consistent has been identified as costly and requires expertise, institutional capacity, funding and time (33). These elements can be in short supply in LMICs, where analytic and administrative capacity is limited, funding and human resources are scarce, and governments may be hesitant to restrict their own discretionary powers (34).

The role for civil society in African subregional systems

We set out to demonstrate the importance of a meaningful role for civil society in going forward in Africa. The AU is working with multiple partners including the European Medicines Agency (EMA), national regulators in Europe and elsewhere, and funding partners to leverage international experiences in moving forward with the AMA (16). The African Pharmaceutical Technology Foundation is being set up under the auspices of the African Development Bank to promote and broker alliances between foreign and African pharmaceutical companies and others to build collaboration between the public and private sectors, for example African Union Commission, European Union Commission, WHO, the World Trade Organization, Medicines Patent Pool (MPP) and other philanthropic organisations, bilateral and multilateral agencies and institutions (10). We argue that local communities are important stakeholders in access to medical products and have a clear participatory role in the medical product lifecycle in Africa. Drivers for participation include equality and equity, dealing with stigmatisation, ethics and morality, and the need to sustainably support national governments to deliver effective health services. Discussion is needed on facilitators for patient, civil society and community engagement and ways in which the concerns of governments and other stakeholders can be addressed.

Human rights and social cohesion

The WHO sees that the purpose of healthcare innovation as to deliver new and improved health policies, systems, products and technologies, services and delivery methods (35). The United Nations (UN) has set a goal for Universal Health Coverage (UHC) in LMICs as part of the 2030 Agenda for Sustainable Development (36). The WHO took up the challenge of equitable access to core essential medicines in all countries of the world by developing a regularly updated, evidence-based essential medicines list (EML) to focus activities including manufacture at a country level (37). The EML can, however, be seen as limiting the availability of medical products for some people where treatments may not be on the list causing individual countries to be challenged to look at how they can extend their EMLs to new potentially effective treatments, for example in Thailand (38). This is particularly so for people with disabling and life-threatening diseases, such as cancers and rare diseases, where people become aware of the new treatments through international patient networks (eg 39, 40), industry alerts and access schemes (eg 41, 42). Human rights can be seen to offer an important mechanism for citizens to petition for additional government resources and for delivery on health services considered high priority. International Human Rights law demands the fulfilment of 'core obligations' by states including for national strategies across entire populations with plans of action based on burden of disease and through a legitimate and participatory process

(43). As an example, people living with a rare disease are at greater risk of stigmatisation and discrimination, creating obstacles to their full participation in society. The United Nations General Assembly in 2021 adopted a Resolution on 'Addressing the challenges of persons living with a rare disease and their families' to promote and protect the rights of everyone living with a rare disease (44).

Risk management, actions

As part of the regulatory lifecycle, health technology assessment (HTA) is used by a country or region to determine the value of a medical product within its health system (26, 32, 38, 45). HTA with its multi-stakeholder involvement can inform decision making on reimbursement and universal health coverage (UHC) in a way that can be used to resolve policy issues, including right to rescue arguments (46). Incorporating evidence from the disciplines of social and behavioural sciences can enrich the regulatory lifecycle approach and enhance the value of the evidence to inform policy (4). HTA can also bring greater monetary benefit compared with a first come, first served approach, as shown for Thailand (47). Regulatory methodologies continue to evolve and it has become apparent during the Covid-19 pandemic that regulatory and HTA bodies can be more effective if they work together, with clinicians and civil society involved throughout (48, 49). There is a good opportunity in LMICs, where capacity is needed, to design purpose-built systems (49, 50). Recent publications have highlighted the important role of patient and public involvement in economic modelling for HTA in the United States (51–53). Patients and civil society can bring their experiential knowledge into model development and evaluation of the clinical safety and efficacy and the quality of the evidence as part of the economic assessment where more complete effectiveness is a prime target.

Medical product supply

Medical products are generally developed for market by industry, and sold as national private goods. We have used the term medical product to be inclusive of innovative technologies under development, including diagnostics and medical devices. Overall, the 'supply' side (innovation policy-makers, entrepreneurs, investors) in high income countries does not align with the 'demand' side (health policy-makers, regulators, value assessors/health economists, payers) and the needs of patients or community. And clinical trial data is also not shared transparently or well (54) in an environment where 'value' means different things to each of the key players in a health system. Responsible innovation principles would address societal challenges in alignment with the objectives of UHC while enabling health innovation (4), where moral, political and power relationships come into play in determining access and use of new technologies (18).

Innovation in medical product supply

Large, global pharmaceutical companies have changed their business models over recent decades. Companies may no longer operate their own drug-directed research laboratories but buy in scientific and technological advances. Early-stage medical products or ideas can come from publically funded research in universities and public research institutions as well as small enterprises (19b, 22), for example much of the foundational work on mRNA vaccines was conducted at universities over many years. This situation has led to the concept of socially responsible licences for inventions emerging from public research, where companies could then use their infrastructure, skills and expertise in developing scientific advances into medical products for use in health systems.

Furthermore, the boundary between basic biomedical research and clinical studies on treatments for disease has narrowed, where seriously ill patients are keen to seek the latest scientific developments in an attempt to extend their lives. As the complexity of the medical products and their development increases so does the cost of medical products, making them less accessible to those in need of treatment, and challenging the sustainability of health services (55, 19). In closed, regulated markets, it is important that medical products are assessed for safety and performance, and to determine their value and benefits to a healthcare system constrained by a finite health budget. Innovation is generally associated with profitable business models where it is predicted the product will have health benefits for a particular disease area. Pharmaceutical companies have an obligation to their shareholders to increase their markets. They do not have to ensure that technologies entering the market are either desirable or cost-effective (56, 57) such that not all innovative medical products or technologies add value nor are sustainable for healthcare systems. It is to their benefit to be the first company to bring a new medicine type to market, and so they reap economic value from the regulatory process (56). Other companies develop similar products, eventually leading to many products in the same therapeutic area. Marketing skills, how the drug is delivered and side effect profiles as well as costs, play a role in how the market evolves. Confidentiality of data on the new medical product is therefore important. On the other hand, the pharmaceutical industry has responsibilities to respect human rights, and to be held accountable (2, 58).

Corporate responsibilities

The Fair Pharma Scorecard is a project of the Dutch-based non-profit organisation Pharmaceutical Accountability Foundation (PAF) that takes action against unreasonably priced medicines and abuse of market exclusivity rights to keep prices high. The scorecard ranks pharmaceutical companies on how well their policies and practices reflected a commitment to human rights principles during COVID-19 (59). The information is used to inform the public and take legal action, if necessary.

Collecting patient and community experience data is key to person-centred health care and medical product and technology development. Industry, regulators, research foundations, patients and communities are actively working to improve the use of meaningful patient experience data in medicines development in the US, Europe, and more widely (60, 61). The Council for International Organizations of Medical Sciences (CIOMS) is an

international, non-governmental, non-profit organization with the mission to advance public health through guidance on health research and policy including ethics, medical product development and pharmacovigilance. It has released a report on systematic patient involvement in the development, regulation and safe use of medicines, incorporating views gathered from an open multi-stakeholder international meeting in Switzerland and a workshop in Uganda (61).

An increasing number of pharmaceutical companies are setting up schemes to provide their products to low-income countries on a 'not-for-profit' basis. These companies include GSK, for infectious diseases (62), Sanofi in therapeutic areas such as diabetes, cardiovascular disease, tuberculosis, malaria and cancer (63) and Pfizer covers medicines and vaccines that treat infectious diseases, certain cancers and rare and inflammatory diseases (64). The latter states that it will work with countries "to identify quick and efficient regulatory pathways and procurement processes to reduce the longer amount of time it can take to make new medicines and vaccines available". It is aligned with the Bill & Melinda Gates Foundation for new vaccines (64). After providing access schemes for new medicines, companies then consider it is up to governments to provide the medications to patients in the longer term (64).

Stakeholder engagement, responsiveness, social value and the needs of civil society

HTA appraisal of the evidence on medical products or technologies and therefore their value is conducted by interdisciplinary multi-stakeholder groups, often using explicit analytical frameworks (65). Engagement with relevant stakeholders, with clear roles and responsibilities, can ensure ownership of the regulatory lifecycle approach. The level of buy-in from each stakeholder, including patients, is crucial for successful implementation of decisions and offers a clear mechanism to look at country or region specific needs and values (66). A 'window of opportunity' is provided to gain political and public support for evidence-informed decision making using legitimate, well-defined evidence-informed processes that are legally defensible (67). This requires engaging patient communities early and in a gender-sensitive, ethical, culture-appropriate and sustainable way (25). An important hurdle to overcome is a lack of trust between the relevant stakeholders (policy makers, administrators, researchers, industry, clinicians, civil society including patients and communities) and to recognise and address inherent vested interests (50). The WHO 2021 Manual for UHC provides guidance on community engagement, starting with formalising structures to create a safe space established within a legal framework. A common understanding among relevant stakeholders is needed of what the participatory space is and will be, with functional guidance on roles and responsibilities (29). The need for mutual respect is of prime importance, allowing trust in the processes to develop over time. Community benefits of participation need to be evident and with a clear understanding of roles and implementation of the decisions to be made.

Some of the issues to be addressed on patient and community engagement are given in **Table 1**, together with possible ways of mitigating them. The table is a collation of the literature and experiential expertise, drawn together by the authors. A working version was shared for comments to known patient advocate leaders with good knowledge of HTA. We have not stratified the issues based on impact or risk as we see that as part of future work, when the context has been established.

A participatory approach

Rights are a source of power if enabled. A participatory space for patients, communities and civil society would bring power to those who have less of it, and for those whose voices are generally weaker and whose health is often poorer (29). A culture of engagement and participation is most effective when backed by legislation affirming the right to health and participation and providing a legal framework to build capacities in fair and transparent participatory processes. The patient, community and civil society population would benefit by being instilled with a sense of social cohesion and duty to participate, to achieve recognition of their roles with meaningful outcomes. A culture of participation relies on development of trust and respectful relationships, across all participants. A provision which is often left out of participatory models is the need to build the capacity to enter, engage with, and maintain a participatory space for communities and civil society organisations – enabling requisite training, coaching, and supervision (29). The level of grassroots and civil society activity evident today provides an indication that the time is ripe for legislation to provide a 'participatory space'. We need to capitalise on the capacity and experience of those who are already active, and take into account their knowledge and local expertise, as with IAPO (39). The African Medicines Agency Treaty Alliance (AMATA) was set up under IAPO as a multi-stakeholder alliance to advocate for the ratification and implementation of the AMA Treaty and provide meaningful engagement with patients and other relevant parties in all aspects of its work (65). AMATA has a Steering Committee that comprises of representatives from its members, patient groups and civil society organisations, NGOs, industry associations, research and academic networks, youth and advocacy groups (68). Another example is the World Patients Alliance, where patient and community groups intermingle with other such people across the globe to address patient safety (69). A civil society that is educated to world-class standards, with the ability to adopt and professionally adapt technical expertise is important in moving forward. Collaborative programs and exposure to other international bodies and study programs can help with this if aware of the unique context of the African region and the need for decolonialism.

Contribution to the field

Low and middle-income countries in Africa did not have access to COVID-19 vaccines that were available to high income countries early in the pandemic. This has demonstrated that the Africa region cannot rely on charity to meet its preventive and therapeutic needs.

TABLE 1 Collated identified issues for meaningful civil society engagement with multi-stakeholders, and possible mitigating strategies, based on the literature and experiential knowledge.

Issues for civil society engagement	Mitigating strategies
The need for mutual respect, and trust	Must be earned, maintained over time
Communities may not be organised eg into patient and disease-based groups or organisations	Incorporate Real World Evidence and therefore patient experiences (surveys, PROMs, PREMs, patient preference studies). The need to use a range of ways to seek the input and views of diverse patients, carers, families and communities
Economic, educational and power inequalities that can cause distrust	May best be worked on over time by initially involving capable individuals who understand the issues and have a strong connection to patients and civil society
Lack of funding: little or no money, or with budget restraints and the need to support a community in their care	Make a part of usual business to collect information/data on experiences
Lack of understanding of role and responsibilities, processes	Education and training packages, one-to-one conversations, mentoring, train-the-trainer programs
Some communities may have unrealistic expectations of what benefits or compensation and support the community and community partners may receive	Provide transparency about how money is spent and working goals; sharing the concept of a social contract, and longer term goals
Demands from communities—to address the burden of disease that is unrelated to the area of immediate deliberation. For example, factors such as poverty, malnutrition, low (health) literacy, lack of healthcare infrastructure and high disease burden	Slowly develop trust (ideally within a social contract) that people are working toward principles of greater transparency and documented sharing of information and evidence from data collection
A concern that disease-based support groups place their own treatment needs above the needs of other patients	Develop trust (ideally within a social contract) that people are working toward well documented and transparent prioritisation processes
Ethical issues such as any risks of participation or any form of harm, role of gender in representing communities	Working sustainably over time, with good shared documentation of efforts, to equitably meet the needs of the entire community, with cultural awareness
Lack of education, knowledge, training and capacity to be able to engage, targeted at patient/civil society groups, community, individuals	Share good practices
Lack or 'representativeness', particularly within mixed/heterogeneous communities	Encourage organised groups to seek wider perspectives and viewpoints, to report back on
If there any community benefits of participation	Increased understanding of the decisions to be made, and how they are made
Leakage of clinical trial data and information – As each company tries to keep its early trial data as confidential as possible eg in delaying release of clinical trial data and the content of its submissions. This could potentially reduce the competitive edge for a company	Upskilling on need for confidentiality with the knowledge that stakeholders are respectfully working to achieve the goals of a participatory approach to decision making in health care
Engaging patient groups with financial relationships with industry, which might lead to conflict of interests and subsequent potential threats to the integrity and independence of the stakeholder groups	Transparency about corporate funding. Need to build on transparency about corporate funding – need to address in whatever way can, and with all stakeholders so all potential conflicts become evident
'Expressiveness' is intertwined in one's culture, experiences, values, and self. Need to create the participatory space and invite patients, communities and civil society in	Provide space for the many voices, faces, and mannerisms
Takes resources and effort	Upskill, monitor and evaluate – to enable continuous improvement

International Human Rights have not protected its populations. Donated products are often of inferior quality when received, which adds to the need for strong regulation, value assessment and appropriate actions for medical products within the regulatory lifecycle. The newly formed African Medicines Agency and African Pharmaceutical Technology Foundation could have important roles. Civil society participation in health care and medical product decision making is written into International Human Rights, and country governments as well as industry have duties and responsibilities to uphold these rights. We outline concerns that have been raised in involving patients, communities and civil society as meaningfully and actively participating stakeholders within the regulatory lifecycle, and steps for building mutual respect and trust. Solidarity and social cohesion are important in moving forward to ensure that medical products are effective, safe and affordable and available to the people who need them.

Conclusions

African countries have learned through the COVID-19 pandemic that they cannot rely solely on charity to provide essential medical products in a timely way. In line with International Human Rights, Africa needs to strengthen its own biopharmaceutical and regulatory lifecycle industries. With solidarity and social cohesiveness the region can develop its own manufacture and increase access and negotiating power for medical products and technologies. Regional change is needed to build sustainable participatory health systems that have strong regulatory lifecycle structures to meet therapeutic needs, building expertise and capacity aligned to local needs through a participatory approach that meaningfully involves patient, communities and civil society together with other key stakeholders. We have outlined some of the background issues together with concerns and ways to address them in promoting patient,

community and civil society participation in regulatory lifecycle policy, value assessment and decision making.

We have a human right to health and essential medical products, but the drive for innovation has exaggerated inequities in delivery of health care and added to ever-increasing complexities and costs in a market where products developed by industry are sold as national private goods.

Collating patient and community stories and data on experiences with healthcare services and medical products is key to person-centred health care, and in medical product development and value assessment. Global biopharmaceutical companies are setting up not-for-profit schemes to provide their medical products to low-income countries. But sustainable health programs ultimately require states to take over management and funding of the programs that provide these services. Understanding health as a human right creates a legal responsibility for countries to ensure access to timely, acceptable, affordable health care of appropriate quality, in addition to addressing other social determinants of health. An important feature of human rights is meaningful participation by civil society across the regulatory lifecycle, policy and value determination in a gender-sensitive, ethical, culture appropriate and sustainable way.

Community benefits of participation may become evident with clear understanding of roles, processes and responsibilities for implementation of decision making.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for this study in accordance with the local legislation and institutional requirements.

Author contributions

All authors discussed the concepts to be included and together conceived the manuscript. JLW wrote the manuscript and all authors reviewed and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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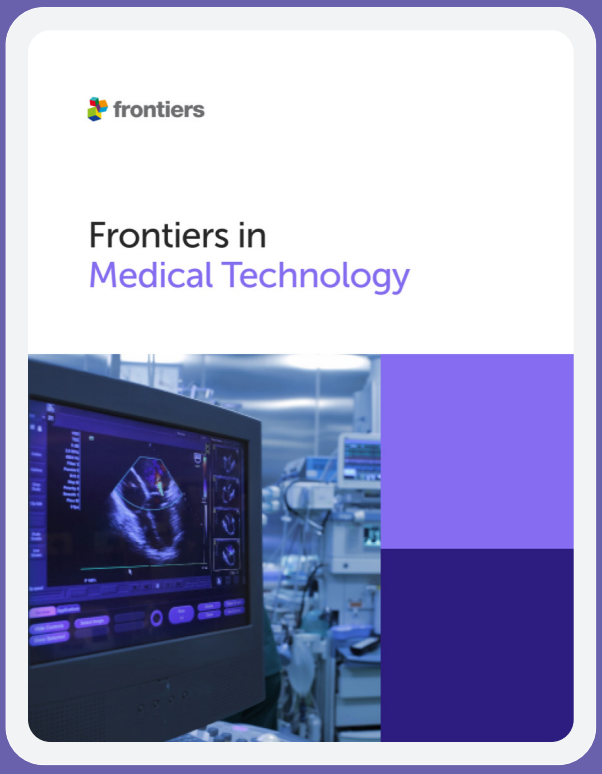

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