reduced-dose versus full-dose direct oral anticoagulants was not met statistically, the 5-year cumulative incidence of recurrent venous thromboembolism of around 2% in either treatment group is reassuringly low, and a potential inferiority of the reduced dose lacks clinical relevance in the context of these low absolute risks. Therefore, we are interested in the benefits in terms of safety and net clinical benefit. Although Couturaud and colleagues[7] designed the RENOVE trial to allow testing for superiority of safety only if non-inferiority for efficacy was met, we believe that the data on bleeding speak for themselves. The RENOVE trial showed a risk reduction in major and clinically relevant non-major bleeding of 39% with the reduced dose, with clinically relevant differences in 5-year cumulative incidences between the full dose and the reduced dose. We hypothesise that the RENOVE trial was able to show this difference due to the median duration of follow-up of 36 months, in contrast to the previously executed trials that followed up patients for 12 months.[4,5]

The RENOVE trial is an example of investigator-initiated studies addressing crucial knowledge gaps.[8] Although already widely implemented, this is the first study that provides robust evidence that reduced-dose apixaban or rivaroxaban for the extended treatment of patients at high risk of recurrent venous thromboembolism is the safest option in the long term, although this remains uncertain for subgroups of patients, such as those with obesity or cancer.

SM reports receiving honoraria from AstraZeneca, Alveron, Bayer, Hemab, Norgine, Sanofi, Sirius, VarmX, and Viatris for advisory or data safety monitoring boards, or educational activities, all outside the submitted work. All honoraria are paid to her institution. JL reports receiving honoraria from AstraZeneca, Viatris, and Bristol Myers Squibb–Pfizer for advisory boards or educational activities, all outside the submitted work. All honoraria are paid to her institution.

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20th anniversary of the WHO Framework Convention on Tobacco Control coming into force: time for a step change in ambition

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Feb 27, 2025, marks the 20th anniversary of the WHO Framework Convention on Tobacco Control (FCTC) coming into force. This legally binding international treaty, the first negotiated by WHO, rapidly became one of the most widely embraced in UN history. The 183 parties to the FCTC, covering more than 90% of the world's population, have committed to "preventing and reducing tobacco consumption, nicotine addiction and exposure to tobacco smoke"[1] through implementing the measures in the treaty. As the treaty enters its 21st year, we reflect on its achievements and identify the need for a step change in ambition if the treaty is to continue to effectively address the tobacco epidemic, alongside the emergent nicotine and multiple product use (poly-use) epidemics.

The FCTC's achievements are impressive: an acceleration of tobacco control policy implementation and declines in the prevalence of tobacco use (including smoked and smokeless tobacco) in every country income group and globally, from 29·3% in 2005 to 20·9% in 2022.[2,3] These outcomes reflect the fact that the treaty focuses on population-level approaches to reducing tobacco use and specifically addresses the tobacco industry as the vector of the epidemic through Article 5.3, which requires parties to protect their public health policies from the vested and other commercial interests of the tobacco industry.

While this success should be promoted, there is a need to recognise that 44 parties have yet to implement a single FCTC measure, and many have only achieved partial implementation.[2] Insufficient political will and low financial and workforce resources for treaty implementation have been ongoing challenges, but the single greatest barrier to implementation has been the tobacco industry.[4]

The opposition of transnational tobacco companies (TTCs) initially took the form of immense pressure against the treaty ever coming into existence. This was followed by an ongoing fight—country by country and policy by policy—against implementation, including by threatening expensive legal challenges.[5] TTCs now have two additional approaches. First, to filibuster during the biennial Conference of the Parties meetings (COP, the decision-making body of the FCTC) by getting industry actors included on government representations in defiance of treaty rules.[6] Second, to claim that, by virtue of now selling e-cigarettes and other new nicotine and tobacco products, they have "transformed" into companies committed to "harm reduction" and therefore deserve

***Panel:* Recommendations for change to improve and strengthen FCTC implementation**

Accelerate implementation

Countries that have yet to implement any policies should be supported to move to best practices, skipping incremental approaches. The FCTC 2030 project[19] provides a successful model which, with adequate resourcing, could support such countries. For countries that have reached top-level implementation, the Expert Group report on forward-looking measures (Article 2.1) is expected to provide ways to achieve greater gains and to ensure the treaty acts as a floor, not a ceiling.[17]

Deal rapidly with new products and industry misinformation in this area

There is unlikely to be a single approach to harm reduction or new product regulation suitable to the contexts of all 183 parties, not least because high regulatory capacity will be essential if such approaches, most relevant to countries that have fully implemented FCTC measures, are to work.[7]

To attempt to achieve a single approach through the FCTC would, therefore, be a distraction from the population-level approaches that characterise its success. Instead, parties should recognise that: genuine harm reduction, not that promoted by industry, involves reducing harm at individual, community, and population level; all FCTC regulations can be applied to new products (Article 5.2), and that countries can also go beyond this through, for example, bans on importation of new products and devices in line with Article 2.1 of the treaty.

Address industry interference

Improve Article 5.3 implementation across the whole of government: the changing tactics of TTCs indicate that Article 5.3 is more important than ever.[6,7] Although previous COP decisions highlight the need to protect policies from interests beyond tobacco, future decisions could further clarify and expand this to future-proof Article 5.3 from further industry changes, including investments in pharmaceuticals. There is a need to recognise that conflicts of interest exist independently of the product because the role of industry—to maximise shareholder value—does not align with the role of government—to act in the public interest. This wider conceptualisation of conflict of interest could also enable more effective whole of government implementation of Article 5.3 and reiterate that Article 5.3 is applicable to all aspects of the treaty, including those led by non-health ministries that the tobacco industry targets.[5]

Steps must be taken to challenge countries that allow industry representation on their delegations. International cooperation, notably within regional groups, must be harnessed to apply pressure against such behaviour. FCTC parties' declarations of interests, currently voluntary, should be made mandatory and public (allowing external scrutiny). Procedural reforms could establish time limits that restrict the ability to filibuster.

A legal defence fund needs to be resourced. TTCs frequently threaten litigation against tobacco control policies. Even when unfounded, this exerts a chilling effect, particularly in low-income and middle-income countries.[5] The successful defence of Uruguayan legislation through philanthropic funding illustrates the important role of an accessible defence fund.[20]

Fund independent science. The tobacco industry uses science and data as a weapon. With the tobacco industry a dominant funder of research, including on illicit tobacco and new products, and industry-funded work often shown to be poor quality and misleading,[21,22] funding for independent science is essential to address industry interference and misinformation.[22,23]

Article 19 on liability needs to be harnessed to hold the tobacco industry to account for all aspects of tobacco industry-created harms. This can include both preventive and deterrent actions, such as recovering health-care and environmental costs, imposing harmonised steep financial penalties, and establishing compensation funds through mandatory industry contributions.[24]

Increase intergovernmental cooperation

Articles 20–22 promote scientific and technical cooperation between parties, yet more timely and effective sharing of knowledge between parties could enable greater progress through, for example, sharing of data and regulatory experience to counter tobacco industry misinformation, and collaborating on research on novel approaches to encourage innovation.

FCTC=WHO Framework Convention on Tobacco Control. COP=Conference of the Parties. TTCs=transnational tobacco companies.

a place at the policy table.[7,8] These claims, promoted via public-relations campaigns and industry-favourable science, have created confusion over harm reduction and tobacco control more broadly.[7] However, TTCs have not transformed.[7,8] Instead, with global cigarette sales declining and their financial outlook threatened, TTCs added additional highly addictive products to their portfolio, marketing them to young people to create new epidemics, while continuing to maximise cigarette sales and oppose tobacco control measures.[7–9]

This response to the FCTC's success was inevitable: TTCs remain incentivised to maximise profits and able to externalise the costs of the harm they cause to others, thus making excess profits.[10,11] Consequently, individuals, communities, and governments have to meet the costs of the industry's health, environment, and supply-chain harms, while the TTCs' excess profits are channelled against public health policies and other efforts to hold them to account.[10,11] As with other forms of corporate-driven health and environmental harms, this situation will continue until these underlying system drivers are addressed.[10–12]

Unfortunately, the consequence of these actions by TTCs is that tobacco control is now under serious threat: the previous acceleration of FCTC policy implementation and declines in global cigarette sales and tobacco use prevalence have all slowed, the last in every world region.[2,3,7,13] There have been increases in teenage vaping and other forms of nicotine use in many countries, some of which, including England and Ireland, have also seen recent increases in smoking among teenagers and young adults; these increases follow years of decline and can no longer be attributed to lockdowns during the COVID-19 pandemic.[7,14,15] The available clinical and preclinical evidence suggests that exposure to nicotine during crucial periods including adolescence can affect reward-related functions and behaviours, increasing the risk of long-term addictions.[16] Alongside tobacco industry diversification, this evidence on the long-term impacts of nicotine suggests that poly-use, with its accompanied health risks, could become the norm.[7]

At the 20-year mark, the FCTC is therefore at an unavoidable inflection point. If a generation of young people is to be protected and progress restored, parties to the FCTC must step up their ambition. The panel details specific recommendations to accelerate progress across parties at all stages of implementation, address the changing nature of the tobacco and nicotine epidemics, and better counter industry interference.[17–24] We detail how this can be achieved by harnessing recent COP decisions[17,18] and the treaty's original ambition to address global challenges through cooperation and collective action.

Ultimately, however, sustainable financing needs to be secured for such recommendations and the system drivers of the tobacco and nicotine epidemics need to be addressed—externalities, excess profits, and the consequent resource imbalance between industry and those attempting to hold them to account.[10–12] By moving towards a polluter pays approach, in which the tobacco industry pays for the harm it causes, both can be achieved. This can be realised at the national level through implementation of FCTC Article 19 (liability) or Article 6 (price and tax measures). For example, in addition to tobacco excise duties, which fall on tobacco users, Article 6 can be used to implement more innovative fiscal tools such as surtaxes, solidarity levies to create tobacco control funds,[25] or price caps[26] to generate revenue and reduce the profit incentive, which fuels industry behaviour.[27]

More uniquely, however, FCTC Article 26 provides a mechanism for developing a collaborative multi-national approach to achieve these aims through similar approaches. Tobacco companies engage in all forms of profit tax avoidance through intercorporate transactions, such as transfer pricing, and excise tax evasion through involvement in global cigarette smuggling.[28,29] TTCs funnel money from resource-poor countries, where their health, environmental, and production supply-chain harms increasingly accrue, to shareholders in richer nations.[30] A levy applied to TTC international financial transfers could address these transnational inequities and provide reparation for the damages caused, while simultaneously addressing the drivers that fuel the tobacco epidemic. Funds raised could be administered by the FCTC Convention Secretariat and allocated according to need to build capacity and fund legal support, independent science, and tobacco industry denormalisation campaigns, among other measures detailed in the panel. At the next COP, in November, 2025, a group could be established to propose the best system, drawing on existing work and international financing mechanisms such as the polluter pays systems established for maritime oil spills.[27] Only if such a financing system is mandatory can the industry be prevented from evasion or positioning itself as part of the solution.

As preparations for COP 11 begin, parties must harness the leadership and energy necessary to realise the FCTC's full potential. Addressing the system drivers of the tobacco epidemic is essential to achieving this. Given the enormous societal and health costs of the tobacco epidemic, they cannot afford not to do so.

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Challenges in undertaking research in transplantation

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In just over 60 years, transplantation has evolved from an experimental procedure to the treatment of choice for patients with end-stage organ failure. This achievement is the result of arduous research in many fields including immunology, surgery, and medicine, often relying on the use of donated organs. It is also the result of successful translation of experimental procedures and new knowledge into routine clinical practice, even when innovations have challenged societal, ethical, and philosophical norms.[1] These innovations[2] have also highlighted the difficulties in undertaking groundbreaking research that necessarily involves not only the patients receiving organ transplants but also the donors of these organs.

In the setting of deceased donation and transplantation, the use of organs and tissues for research, and the design, conduct, and outcomes of research involving deceased donors often pose complex and unique ethical challenges.[3] The first one stems from the quasi-inevitable reliance on substitute decision makers for consent to donor-related research, which can be a considerable burden for grieving and fatigued donor families. In addition, decision-making about the involvement of potential donors in research could be complicated by legal uncertainty regarding authority for decision-making on their behalf.[4] Striking the right balance between extensive disclosure of information and avoiding distress or burdening substitute decision makers is challenging. Some families could prefer not to receive detailed information about research procedures but this could lead to consent for research being presumed without specification in circumstances in which it might be reasonable to know key details, such as substantive interventions in the donor's body. To address these challenges, consent for research should be streamlined and organ donor registries could be used to record it.

Secondly, when research involves deceased donors, especially where interventions could be performed before death or during the dying process, there could be fears that the quality of end-of-life care for donors, and their families, could be compromised. Deceased donors could be regarded as not being research participants and, as such, they are vulnerable to exploitation in research because of a lack of robust consent. For example, in the USA, routine ethical governance of human research only applies to research involving living people, such that studies including deceased donors might not require ethical scrutiny by an institutional review board.[5]

Concerns could also arise due to uncertainty regarding ethical governance of some types of trials, and inconsistencies between legal frameworks governing decision-making for donation, substitute decision-making for clinical care, and research.[6] In some jurisdictions, the person with legal authority to make decisions about clinical treatment and, potentially, research, on behalf of an individual lacking capacity could be different from the person legally authorised to make donation decisions, as decision-making in those two contexts is governed by different legislation.[4]

Furthermore, differences between the legal and clinical standards for the determination of death[7] within and between jurisdictions could complicate efforts to harmonise research protocols in multicentre trials while ensuring compliance with relevant laws. For example, legislative definitions of death as the irreversible loss of circulation could conflict with clinical standards for death determination based on permanency rather than irreversibility.

Donor interventions studies are further compounded by the potential detrimental effect on the organs that might not be the primary target of the intervention,[8] which challenges the determination of risk-benefit thresholds as