



Strategies used to access CFTR modulators in countries without reimbursement agreements[☆]

Jonathan Guo^{a,*}, Grace Hennessy^a, Benedict Young^a, Andrew Hill^b

^a School of Public Health, Faculty of Medicine, Imperial College London, United Kingdom

^b Department of Pharmacology and Therapeutics, University of Liverpool, United Kingdom

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ABSTRACT

CFTR modulators represent the international standard of care for the treatment of cystic fibrosis (CF). Yet due to prices of over \$250,000 per year they are functionally inaccessible for people with CF (pwCF) unless reimbursed by healthcare systems. Current prices are unaffordable for payors in almost all low- and middle-income countries (LMICs) worldwide, and resulting disparities in access are widening existing global health inequities. In comparable situations in other therapeutic areas, patients have successfully developed strategies to bypass national reimbursement systems and gain access to treatment. We therefore undertook an international survey of CF clinicians in 15 countries where CFTR modulators are not reimbursed, to characterise alternative means of accessing modulator therapy.

Successful methods were identified in 11 countries, and could broadly be categorised into legal challenges to access originator modulators, use of generic formulations, and access via donations. Aside from domestically produced generics used in Argentina and an originator-led donation program in Ukraine, these methods were only able to provide treatment to limited proportions of the local CF population due to significant associated financial costs. Accordingly, they are generally not sustainable or widely applicable, and fail to address the underlying structural issues driving international disparities in access.

Twelve years after the initial marketing of CFTR modulators, pwCF in LMICs are being forced to take extraordinary measures to access disease-modifying treatment. Corrective measures are urgently required to overcome barriers posed by restrictive patents and prohibitively high prices, and to promote global health equity for pwCF.

1. Introduction

Due to their high costs, CFTR modulators are inaccessible for people with CF (pwCF) unless funded by healthcare payors; typically through reimbursement agreements with the patent holder, Vertex Pharmaceuticals. Nevertheless, list prices of over \$250,000 per year render them unaffordable for health systems in almost all low- or middle-income countries (LMICs) worldwide [1,2].

Resulting inequities in treatment access are exacerbating pre-modulator global health disparities [3]. With patent protections for elexacaftor/tezacaftor/ivacaftor (ETI) expected to remain in place until at least 2037 [4], these are likely to persist for the foreseeable future, and widen further with successive advances in modulator and gene

therapy.

Similar barriers in other therapeutic areas led to the development of alternative routes to access that bypassed health systems altogether. For example, buyers' clubs for HIV and Hepatitis C treatments, which were able to provide access for large numbers of patients, alongside pressure for broader policy changes [5,6].

Accordingly, we sought to characterise strategies used by pwCF to access CFTR modulators in countries without formal reimbursement agreements, and to evaluate their applicability to improving treatment access globally.

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* Corresponding author at: Department of Primary Care and Public Health, Imperial College London, White City Campus, 90 Wood Lane, London W12 0BZ, United Kingdom.

E-mail address: jyg17@ic.ac.uk (J. Guo).

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2. Methodology

An international survey of CF clinicians, including those involved with quality improvement in relevant countries (e.g. via twinning schemes), was conducted through email communications and virtual interviews. The initial survey and all subsequent communications were conducted in English, and relevant questions/topics can be found in Appendix 1. Countries were eligible for inclusion if they had been identified as having a diagnosed CF population of ≥ 200 people in previous research and no agreed reimbursement deal for CFTR modulators (Fig. 1) [7]. In countries meeting the population threshold, reimbursement status was assessed using national drug registries alongside manufacturer/patient organisation press releases, and confirmed as part of the survey.

Of a total of 95 countries where pwCF had been identified [7], 15 met inclusion criteria, and 32 clinicians were contacted between February and November 2024. An initial cohort of 28 clinicians was identified through collaboration with patient organisations, literature searches and previous research [7], with a further four generated via snowball sampling. During data collection, there was also one instance of direct outreach from a clinician in Uruguay.

Each identified strategy was categorised according to underlying mechanism. Following this, the number of patients successfully accessing CFTR modulator therapy in each country was compared with estimates of the diagnosed patient population, in order to facilitate comparison between jurisdictions and characterise the efficacy and generalisability of individual strategies.

3. Results

Data were provided by a total of 17 clinicians representing 13 countries, with a collective estimated diagnosed population of 13,692 (Table 1). Methods of successfully accessing CFTR modulators were identified in 11 countries (Fig. 2), generally only providing treatment to small proportions of the diagnosed population.

3.1. Legal applications

Originator modulators were accessible via legal action against government bodies or insurers in Chile, Colombia, Türkiye and Uruguay, typically on the basis of the human right to life and health [8]. In Chile, Colombia and Türkiye patients must undergo iterative applications to access successive courses of medication, disrupting treatment continuity [9]. Proceedings have also begun in Uruguay for the issuing of a

compulsory license to override patent protections for ETI [10].

3.2. Use of generic formulations

Patent rights have not been granted for CFTR modulators in Argentina [11]. Therefore, generic manufacture is permitted and such formulations are widely available; with access to modulator therapy also enshrined in national legislation [12]. Small numbers of pwCF from Chile, India, Mexico, Türkiye and South Africa also utilised generic modulators, usually via regular personal travel to Argentina. This is due to regulations imposed by the World Trade Organisation's Agreement on Trade-Related Aspects of Intellectual Property Rights that restrict the sale of generic medications into jurisdictions where they are under patent [13]. In South Africa, some patients used "modulator-sparing" treatment regimens as a further cost-saving measure [14].

3.3. Donations

An originator-led donation program was launched in Ukraine in September 2023, providing CFTR modulators to all eligible patients. In Palestine and Jordan, local donations made to individual patients provided limited, irregular access to modulator therapy.

4. Discussion

Our findings present multiple approaches to access CFTR modulators (usually ETI) in the absence of health system reimbursement, and the countries included within our survey represent a significant proportion of the global CF population without treatment access [7]. Yet, a paucity of literature evidence necessitated direct communication with clinicians to gather information.

Therefore, whilst the data collected are highly contemporary, they are not publicly available or auditable. In addition, given the intrinsic nature of the topic, data are liable to change, for example with evolving legal precedents/decisions, or personal financial circumstances. Our analysis excluded 43 countries on the basis of a limited diagnosed population, and for those that were included, we were unfortunately usually only able to contact individual clinicians. As a result, some strategies may have been missed, and estimated proportions of pwCF utilising each mechanism may represent underestimates. However, this is likely mitigated to some extent, as CF care is typically centralised into a small network of specialist referral centres [15], and in comparable situations in HIV and Hepatitis C knowledge sharing amongst patients and clinicians was common [6].

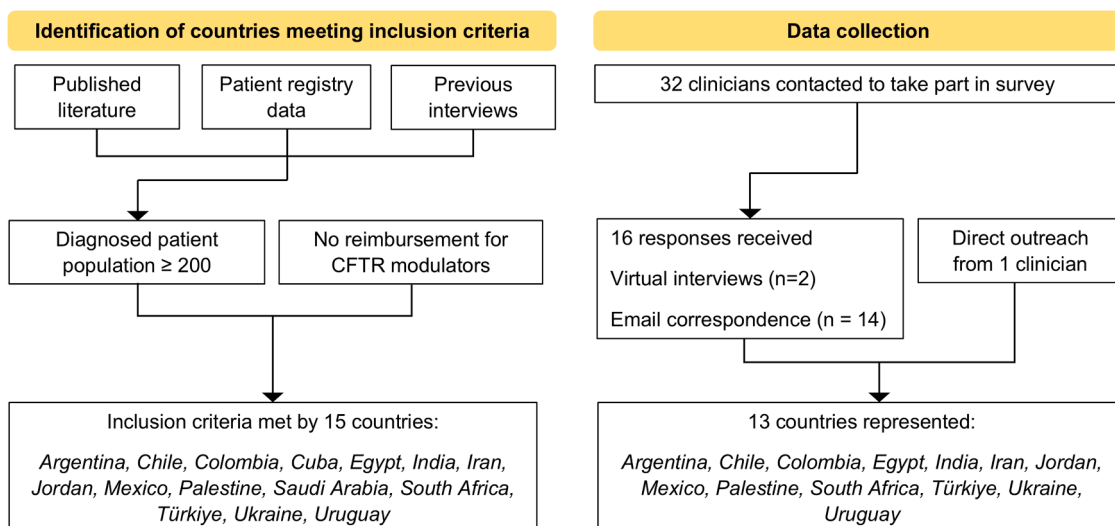


Fig. 1. Flowcharts illustrating processes of country selection and data collection.

Table 1

Table displaying strategies employed within each country to access CFTR modulators, estimated number of patients utilising these and implied coverage of the local CF population. CF = Cystic Fibrosis.

Country	Alternative strategy employed	Estimated number of patients accessing modulators	Diagnosed patient population	Source of diagnosed patient data	Estimated number of patients accessing modulators as a proportion of diagnosed population
Argentina	Local production of generics	1,363	1,836	CF registry	74 %
Chile	Iterative legal applications	90	850	Regional survey	11 %
	Personal importation of generics	<10			<2 %
Colombia	Iterative legal applications	~120	1,008	National registry of rare diseases	12 %
Egypt	–	0	800	Previous research	–
India	Personal importation of generics	5	600	Previous research	1 %
Iran	–	0	3,000	CF registry	–
Jordan	Non-originator donations	1	385	CF registry	<1 %
Mexico	Personal importation of generics	<50	1,050	National survey	<5 %
	CF care in neighbouring country	<15			<2 %
Palestine*	Non-originator donations	~3	290	Previous research	1 %
South Africa	Personal importation of generics	65	526	CF registry	12 %
Türkiye	Iterative legal applications	~450	2,554	CF registry	18 %
	Personal importation of generics	2			<1 %
Ukraine**	Originator donation program	287	585	CF registry	49 %
Uruguay	Single legal application	85	208	National reference centre	41 %

* Pre-conflict data.

** Donation program rollout ongoing during data collection.

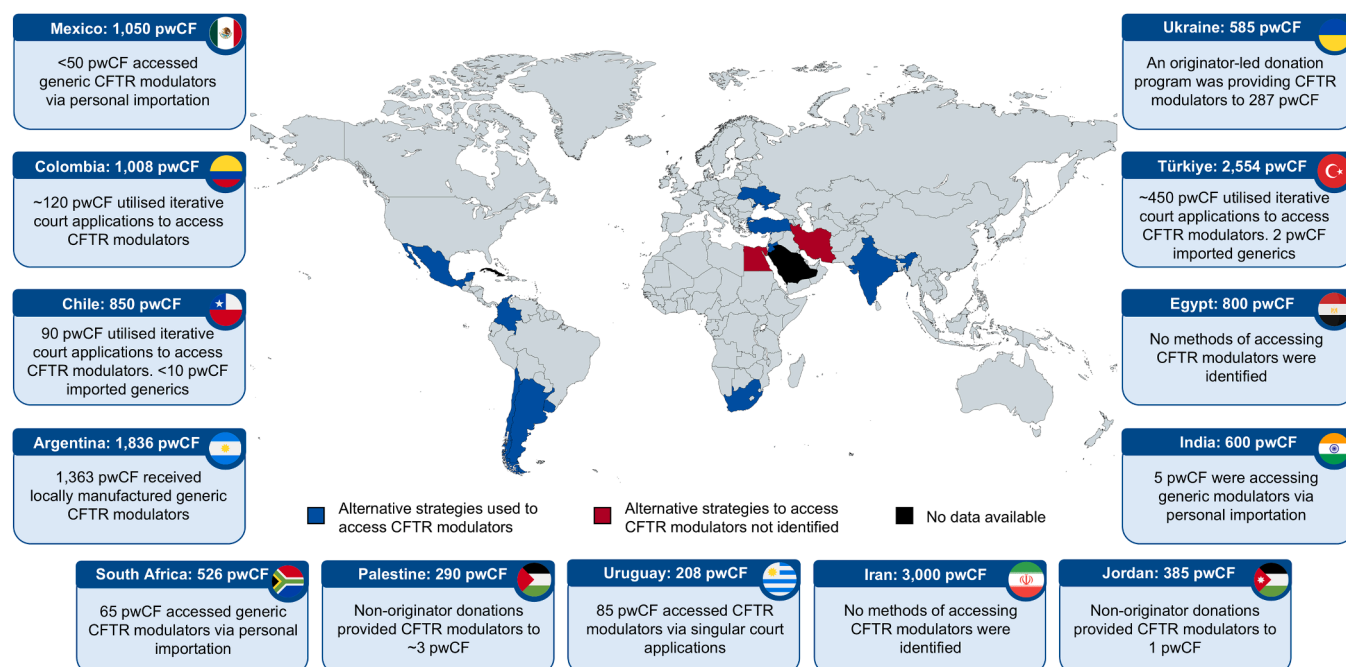


Fig. 2. World map displaying alternative strategies used to access CFTR modulators in countries without reimbursement agreements. Total estimated diagnosed CF population within each country is displayed beside its name. PwCF = people with CF.

Since data collection, an agreement has been made in South Africa providing ETI to pwCF with “top end” medical insurance plans (~30–40 % of eligible patients) [16,17]. Whilst providing some treatment access, this policy stands to counterintuitively worsen health equity for pwCF in

South Africa by further linking health to socioeconomic status. Likewise, the significant costs associated with most strategies identified in our survey (such as for regular international travel, purchase of generic medication out-of-pocket, fees for legal representation) inherently limit

them to those with sufficient financial means.

Moreover, successful legal challenges to gain access to modulators pose significant resource allocation challenges for policymakers in LMICs, as health systems with limited budgets are compelled to purchase and supply medication at close to list prices. For example, since 2023 the government of Uruguay has spent \$22 million to provide ETI for ~80 pwCF, equating to 0.4 % of the country's entire 2021 healthcare expenditure [10,18].

Notably, the only strategies likely to provide sustainable access to large proportions of the diagnosed population are those present in Argentina and Ukraine, demonstrating the importance that policies to improve access are universal in scope and without precondition. The donation program supplying medication in Ukraine has since been expanded to cover a total of 12 countries: Egypt, El Salvador, Honduras, Côte d'Ivoire, Kenya, Lebanon, Nepal, Sri Lanka, Tanzania, Tunisia, Uganda and Ukraine [1]. Notably, despite being selected on the basis of a high documented disease burden, at present just two of the countries within our survey sample are included in this program.

Availability of generic modulators in Argentina has enabled national policies to promote treatment access, and generic Argentinian formulations are fundamental to strategies based upon personal travel and importation. Yet these are currently only produced by two companies, and originator modulators are not marketed in Argentina. Prices are therefore vulnerable to local economic factors such as inflation, and remain too high for these medications to represent a feasible solution at a global scale, highlighting the importance of competitive mechanisms to sustainably improve access. Indeed, competitive generic production introduced through voluntary licensing has been proposed as an approach to improve health equity in CF [3,19], and played a key role in addressing similar barriers in HIV and Hepatitis C [20].

Successes in these areas can and should provide a roadmap of possible solutions for CFTR modulators. For example, in both cases the threat of compulsory licensing was leveraged internationally as a tool to drive policy change [20,21]. Similar proposals are ongoing in Uruguay, and were also made during negotiations in the UK, South Africa, Ukraine and Brazil; with some form of access subsequently agreed in each country [22,23]. As such, this policy could represent a path forward in settings where negotiations for access have failed.

5. Conclusion

Twelve years after initial marketing approval, pwCF in LMICs are being forced to resort to extraordinary measures at high personal cost to gain access to modulator therapy. These are largely not sustainable or generalisable, and fail to address the underlying structural issues that drive contemporary disparities. Accordingly, corrective measures are urgently required to improve global health equity. Lessons can be learned from other disease areas, where international advocacy and significant political will were required to drive change.

Ethical approval

No ethical approval was required as this study used only anonymised secondary data with no patient identifying information.

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Data sharing statement

All data used in this study will be available from the corresponding

author, upon reasonable request.

CRedit authorship contribution statement

Jonathan Guo: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration. **Grace Hennessy:** Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Benedict Young:** Writing – review & editing. **Andrew Hill:** Conceptualization, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jcf.2025.02.010](https://doi.org/10.1016/j.jcf.2025.02.010).

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