Supplementary materials

Supplementary material – 1 - PRISMA Checklist

Selection and topic	*Item #*	*Checklist item*	*Location where item is reported (page)*
TITLE			
Title	1	Identify the report as a systematic review	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge	1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) to review addresses.	1
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or sourced.	3
Search strategy	7	Present the full search strategy for all databases, registers and websites, including any filters and limits used.	3, 15

Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought, and if not, the methods used to decide which results to collect.	3
	10b	List and define all other variables for which data were sought. Describe any assumptions made about any missing or unclear information.	3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4
Effect measures	12	Specify for each outcome the effect measure used in the synthesis or presentation of results.	-
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis.	-

	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	-
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	-
	13d	Describe any methods used to synthesize results and provide a rationale for the choice.	-
	13e	Describe any methods used to explore possible causes of heterogeneity among study results.	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in synthesis.	4
Certainty assessment	15	Describe any methods used to assess certainty in the body of evidence for an outcome	-
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	4
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	4
Study characteristics	17	Cite each included study and present its characteristics.	4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	18

Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group and (b) an effect estimate and its precision, ideally using structured tables or plots.	4, 5
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	-
	20b	Present results of all statistical syntheses conducted.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results for each synthesis assessed.	18
Certainty of evidence	22	Present assessments of certainty in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	6, 7
	23b	Discuss any limitations of the evidence included in the review.	6, 7
	23c	Discuss any limitations of the review processes used.	6, 7
	23d	Discuss implications of the results for practice, policy and future research.	6, 7
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3

	24b	Indicate where the review protocol can be assessed, or state that a protocol was not prepared.	20, 21, 22
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors.	-
Competing interests	26	Declare any competing interests of review authors.	-
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-

Supplementary material 2 - Full search strategy

Search string Embase:

('cystic fibrosis'/exp OR ‘Cystic Fibrosis’:ab,ti,kw)

AND

('child'/exp OR 'infant'/exp OR 'adolescent'/exp OR 'newborn'/exp OR child*:ab,ti,kw OR infan*:ab,ti,kw OR adolescen*:ab,ti,kw OR pediatr*:ab,ti,kw OR paediatr*:ab,ti,kw OR youth:ab,ti,kw OR teen*:ab,ti,kw OR school*:ab,ti,kw OR preschool:ab,ti,kw OR toddler*:ab,ti,kw OR kids:ab,ti,kw OR neonat*:ab,ti,kw OR newborn*:ab,ti,kw OR prematur*:ab,ti,kw OR preterm*:ab,ti,kw OR prenatal:ab,ti,kw OR ‘young adult*’:ab,ti,kw OR ‘younger adult*’:ab,ti,kw OR ‘young people’:ab,ti,kw OR ‘younger people’:ab,ti,kw OR ‘early life’:ab,ti,kw OR ‘early in life’:ab,ti,kw OR ‘early age’:ab,ti,kw OR ‘younger age’:ab,ti,kw OR ‘young age’:ab,ti,kw OR ‘adult’/exp OR ‘adult’:ab,ti,kw OR ‘middle aged’:ab,ti,kw OR adult*:ab,ti,kw)

AND

('patient compliance'/exp OR complian*:ab,ti,kw OR noncomplian*:ab,ti,kw OR adheren*:ab,ti,kw OR nonadheren*:ab,ti,kw)

Search string PubMed:

("Cystic Fibrosis"[Mesh] OR Cystic Fibrosis[tiab])

AND

("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR child*[tiab] OR infan*[tiab] OR adolescen*[tiab] OR pediatr*[tiab] OR paediatr*[tiab] OR youth[tiab] OR teen*[tiab] OR school*[tiab] OR preschool*[tiab] OR toddler*[tiab] OR kids[tiab] OR neonat*[tiab] OR young adult*[tiab] OR younger adult*[tiab] OR young people[tiab] OR younger people[tiab] OR early life[tiab] OR early in life[tiab] OR early age[tiab] OR younger age[tiab] OR young age[tiab] OR prenatal*[tiab])

AND

("Patient Compliance"[Mesh] OR complian*[tiab] OR noncomplian*[tiab] OR adheren*[tiab] OR nonadheren*[tiab])

AND

("Pharmacy"[Mesh] OR "Pharmacies"[Mesh] OR pharmac*[tiab])

Supplementary material 3 - Newcastle Ottawa Scale scores

Study	Selection				Comparability	Outcome			Score	Quality
	Representativeness exposed cohort	Selection of non-exposed cohort from same source as exposed cohort	Ascertainment of exposure	Outcome of interest was not present at the start of study	Comparability of cohorts	Assessment of outcome	Follow-up long enough for outcome to occur	Adequacy of follow-up		
Siracusa *et al* (2015) [4]	Truly representative – data were collected from two accredited CF centers, one pediatric and one adult. ★	NA	Pharmacy refill data, electronic monitoring and self-report ★	Yes ★	Adherence was not adjusted for other confounders.	Record linkage ★	Yes (~ 4 months) ★	All cases were included. ★	6	Good
Platt et al (2023) [8]	Somewhat representative – patients were enrolled if they had filled any medication therapy to treat CF with the health system specialty pharmacy. ★	NA	Pharmacy refill data from a specialty pharmacy ★	Yes ★	Adherence and age ★	Record linkage ★	Yes (36 months for CFTR modulators excluding ETI and 24 months for ETI) ★	All cases were included, some were excluded for different reasons ★	7	Good
Olivereau *et al* (2019) [17]	Truly representative – data were collected from five French CF centers: two pediatric and two adult centers and one mixed center. ★	NA	Pharmacy refill data ★	Yes ★	Adherence, travel time, ppFEV1, gender, age, BMI and chronic P. aeruginosa infection were adjusted for logistic regression. ★★	Record linkage ★	Yes (12 months) ★	All cases were included. ★	8	Good

Mitchell et al (2021) [18]	Somewhat representative – All patients with CF carrying at least one Gly551Asp mutation who had taken ivacaftor at any time since introduction from the Manchester Adult Cystic Fibrosis Centre's patient database. ★	NA	Refill data homecare delivery company ★	Yes★	Adherence, FEV_1, BMI ★	Record linkage ★	Yes (60 months) ★	All cases were included but five patients died, four had been taken ivacaftor less than 5 years at the time of data collection and three were younger than 18 years ★	7	Good
Tesell *et al* (2019) [19]	Representativeness was not clearly described.	NA	Pharmacy refill data, internally managed PA system and Medicaid management	Yes ★	Adherence was not adjusted for other confounders.	Record linkage ★	Yes (12 months) ★	All cases were included. ★	5	Moderate

			information system★							
Mehta *et al* (2021) [20]	Somewhat representative – database included patients from different US geographical regions who are on commercial and public health insurance plans. ★	NA	Pharmacy fill data from national specialty pharmacy ★	Yes ★	Adherence was not adjusted for other confounders.	Record linkage ★	Yes (12 months) ★	All cases were included. ★	6	Good
Suthoff *et al* (2016) [21]	Selected group of employer data.	NA	MSCCD database ★	Yes ★	Adherence was not adjusted for other confounders.	Record linkage ★	Yes (18 months) ★	All cases were included. ★	5	Moderate

Supplement material 4 - Study characteristics of conference abstracts (n=9)

				Adherence				
Author, country, year	**Study design**	**Study population**	**Medication**	**Adherence definition**	**Data source**	**Timing of measurement**	**Adherence outcome**	**Factors associated with adherence**
Sutton, Ireland & UK, 2022 [23]	Multi-site non-interventional study	n = 116 Age: ≥ 12 years SRQs: n = 41 MEMS: ETI n = 16, ivacaftor n = 16.	Elexacaftor/tezacaftor/ivacaftor (ETI) Ivacaftor	MPR ≥ 80%	Pharmacy refill data Self-reported questionnaires (SQRs) Electronic medication monitoring system (MEMS) (only in a subset)	Baseline and 6 months	SRQs: Adherence ETI: 98%-93% MEMS: Adherence ETI: 82.7% Adherence ivacaftor: 83.1% Overall adherence: 82.9%	
Maddison, UK, 2019 [25]		n = 29 Male: n = 14	Ivacaftor		Pharmacy refill data	October 2017 – November 2018	All patients <18 years: MPR = >92% 10 adults: MPR = ≤ 85%	

Williams, Australia, 2015 [24]	Placebo-controlled trial	n = 20 Adult: 100%	Ivacaftor Placebo	Percentage adherence % Self-report data	Pharmacy dispensing data	2 active phases and 6 months open label extension	Adherence (self-report vs. actual) AP 1: 96.7% vs. 97.6% AP 2: 96.9% vs. 96.3% OLE: 94.4% vs. 94.5%

Zhou, USA, 2022 [26]		n = 598 Adult: 100%	Ivacaftor Tezacaftor/ivacaftor & ivacaftor Lumacaftor/ivacaftor	PDC ≥ 80%	MarketScan commercial claims	2019	Mean PDC: 74.1% Ivacaftor: 76.2% Tezacaftor/ivacaftor & ivacaftor: 73.8% Lumacaftor/ivacaftor: 59.6%	Hospitalization, costs
Cristiani, Italy, 2020 [22]	Single-center, retrospective, observational study	n = 20 Male: 55% Median age: 20 years	Lumacaftor-Ivacaftor		Prescription refill history Self-report	October 2016 – July 2019, average monitoring period was 26.7 months	Median MPR: 97% (39-107%) Self-report: 98.5% (50-100%) In 15% (4/20 patients): MPR < 65%	
Witt, USA, 2021 [27]		n = 980	Ivacaftor Lumacaftor/ivacaftor Tezacaftor/ivacaftor & ivacaftor Elexacaftor/tezacaftor/ivacaftor & ivacaftor	PDC ≥ 80%	Retail pharmacy claims	2020	Mean PDC 78.5% ± 2.7 Ivacaftor; Lumacaftor/ivacaftor; Elexacaftor/tezacaftor/ivacaftor & ivacaftor 78.2 – 79.1% Tezacaftor/ivacaftor & ivacaftor 73.0%	Age

McIlvain, USA, 2019 [28]	Retrospective chart review	n = 118	CFTR modulators	0-75 days treatment missed = adherent 76-365 days treatment missed nonadherent	CFTR modulator refill data	1-1-2012 to 31-8-2018	Adherence of patients at the specialty pharmacy: 74% (vs. 40% who did not go to this pharmacy)	
Tao, USA, 2019 [29]	Prospective review compared to retrospective cohort study	n = 65 (children)	Ivacaftor, Lumacaftor/ivacaftor, Tezacaftor/ivacaftor. Dornase alfa, tobramycin		MPR, PDC and percentage of prescriptions sent to and filled by health system SPS.	6 months	Retrospective = MPR: 0.85 PDC: 0.75 Prospective (after implementation of SPS) = MPR: 0.86 PDC: 0.80	Clinic workflow designed to do increase SPS
Álvarez, Spain, 2022 [30]	Retrospective observational study	n = 82 Male: 56.1% Adult: 81.7%	Tezacaftor/ivacaftor Elexacaftor/tezacaftor/ivacaftor Lumacaftor/ivacaftor	MPR ≥ 80%	Electronic prescription records	January 2020 to April 2021	Mean overall MPR: 102.7% ± 11.5 Proportion of adherent patients: 98.7%	

AP, active phase; OLE, open label extension

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