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Development of the Advancing the Patient EXperience (APEX) in COPD registry: a modified Delphi Study

Chelsea L. Edwards PhD[1], Alan G. Kaplan MD CCFP(EM) FCFP[2,3,4], Barbara P. Yawn MD MSc MSPH FAAFP[5,6], Janwillem W. H. Kocks MD PhD[1,7,8], Lakmini Bulathsinhala MPH[1], Victoria A. Carter BSc[1], Ku-Lang Chang MD FAAFP[9], Chester Fox MD FAAFP[10,11], Gokul Gopalan MD[12], MeiLan K. Han MD[13], Maja Kruszyk BEng[1], Chantal E. Le Lievre BPH[1], Cathy Mahle PhD MBA[12], Barry Make MD[14], Wilson D. Pace MD[10,15], Chris Price LLB[1], Asif Shaikh MD MPH[12], Neil Skolnik MD[16,17], David B. Price FRCGP[1,7,18]

Affiliations:

[1]Optimum Patient Care, Cambridge, UK; [2]Observational and Pragmatic Research Institute, Singapore; [3]Family Physician Airways Group of Canada, Stouffville, Ontario; [4]University of Toronto, Toronto, Canada; [5]University of Minnesota, Minneapolis, USA; [6]COPD Foundation, Washington DC, USA; [7]Observational Pragmatic Research Institute, Singapore; [8]General Practitioners Research Institute, Groningen, Netherlands; [9]University of Florida College of Medicine, Gainesville, FL, USA; [10]DARTNet Institute, Aroura, USA; [11]University at Buffalo, Buffalo, NY, USA; [12]Boehringer Ingelheim, Ridgefield, CT, USA; [13]University of Michigan, Ann Arbor, MI, USA; [14]Department of Medicine, National Jewish Health, Denver, CO, USA; [15]University of Colorado, Denver, USA; [16]Thomas Jefferson University, Jenkintown, PA, USA; [17]Abington Jefferson Health, Jenkintown, PA, USA; [18]Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, United Kingdom

Corresponding author: Professor David B. Price, Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen AB25 2ZD, UK; E-mail: dprice@opri.sg; Tel: +65 6962 3627

Running head: The APEX COPD registry Delphi Study

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Abbreviations: APEX: Advancing the Patient Experience; AOMG: APEX COPD Operational Management Group; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; EHR: electronic health record; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; mMRC: Modified Medical Research Council; PRO: patient reported outcomes; PRI: patient reported information; PoC: point of care; PCP: primary care physician

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Abstract [word count: 250/250]

Background: Chronic obstructive pulmonary disease (COPD) is commonly managed by family physicians, but little is known about specifics of management and how this may be improved. The Advancing the Patient Experience in COPD (APEX COPD) registry will be the first U.S. primary care, health system-based registry following patients diagnosed with COPD longitudinally, using a standardized set of variables to investigate how patients are managed in real-life and assess outcomes of various management strategies.

Objective: Gaining expert consensus on a standardized list of variables to capture in the APEX COPD registry.

Methods: A modified, Delphi process was used to reach consensus on which data to collect in the registry from electronic health records (EHRs), patient-reported information (PRI) and patient-reported outcomes (PRO), and by physicians during subsequent office visits. The Delphi panel comprised 14 primary care and specialty COPD experts from the U.S. and internationally. The process consisted of three iterative rounds. Responses were collected electronically.

Results: Of the initial 195 variables considered, consensus was reached to include up to 115 EHR variables, 34 PRI/PRO variables and five office-visit variables in the APEX COPD registry. These should include information on symptom burden, diagnosis, COPD exacerbations, lung function, quality-of-life, comorbidities, smoking status/history, treatment specifics (including side effects), inhaler management, and patient education/self-management.

Conclusions: COPD experts agreed upon the core variables to collect from EHR data and from patients to populate the APEX COPD registry. Data will eventually be integrated, standardized and stored in the APEX COPD database and used for approved COPD-related research.

Introduction

Chronic obstructive pulmonary disease (COPD) is managed predominantly by family physicians, but little is known about how this prevalent disease is managed in primary care, or how primary care management in the U.S. may be improved. Management of this disease is daunting when one considers the sheer size of the population (16 million U.S. adults and rising),[1,2] the continuing rise in COPD-related mortality,[3,4] the high symptom burden experienced by patients,[5] and the cost to the U.S. economy (predicted $50 billion by 2020).[6] The prevalence and burden of COPD are predicted to increase over the coming decades due to continued exposure to COPD risk factors (tobacco smoking, air pollution) and aging of the population.[7] Although the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy provides clear strategies for COPD diagnosis and management,[8] they are often not fully understood nor implemented in primary care practice.[9] COPD remains a disease which is under- and mis-diagnosed, resulting in delayed and/or sub-optimal disease management.[10–12] The question remains, how do we ensure optimum management of COPD patients in primary care?

Both primary care- and patient-related factors make this a difficult question to answer. The issues in primary care include a reticence to diagnose COPD in already multi-morbid patients, the temptation to prescribe antibiotics for patients who present with chest infections/bronchitis rather than delving into a COPD diagnosis protocol, and a lack of understanding (or indeed, availability) of spirometry.[12] The issue of COPD under-diagnosis may be further exacerbated by failure to recognize GOLD Group C patients. These patients are not particularly symptomatic but do experience a substantial number of chest infections.[8] They, therefore, often remain under the care of their family physician and never receive

specialist referral. These issues represent significant hurdles to optimized COPD management in primary care, since establishing and acting on an early diagnosis of COPD is a critical step in reducing the extensive morbidity and mortality of this disease. Large-scale efforts to promote awareness of COPD and encourage early diagnosis have been undertaken, to tackle these issues and others in COPD management (e.g. the National Lung Health Education Program in the U.S.). Patient-related hurdles to optimized COPD management include disease denial (lack of understanding, under-estimation of disease impact), poor adherence, lack of patient engagement and empowerment, variable disease presenting patterns, and cost-related issues.[12]

In order to improve the management of COPD in primary care, it is first necessary to describe the patient population in a standardized way, using variables which are clinically relevant, and which can be practically collected and monitored longitudinally. This information should be relevant to both physicians and patients to encourage therapeutic shared decision-making and ultimately better adherence. A COPD registry is one way to achieve these aims. Registries are well-established tools for tracking and reporting epidemiological disease trends that enable treatment benefits and risks that can be longitudinally monitored. They are also useful to track the natural progression of disease, which may be particularly relevant in COPD where progression is slow, and patterns can be difficult to spot. They have the potential to improve diagnostics and be used to inform treatment algorithms.[13] Although both national and regional COPD registries and patient cohorts do already exist in the U.S. (e.g. the Genetic Epidemiology of COPD (COPDGene),[14] the COPD Patient-Powered Research Network (COPD PPRN),[15] and others hosted by universities and healthcare networks), none are based in primary care. Those based in secondary care focus on patients with more severe disease,

117 missing the milder and moderate severity patients. None have captured information on how
118 patients are managed in primary care in real-life.
119
120 The Advancing the Patient Experience in COPD (APEX COPD) registry
121 (https://www.apexcopd.org/) will be the first U.S. primary care health system-based registry,
122 designed to follow these patients longitudinally, investigate how they are managed in a real-
123 life setting and the consequence(s) of various management strategies. The overall aim is to
124 improve primary care for patients with a diagnosis of COPD by capturing clinically-relevant
125 and high-quality data using a standardized set of variables, from multiple sources, in sufficient
126 numbers of patients to ensure representativeness to the wider COPD population, and to
127 answer key research questions relating to COPD in primary care. The registry plans to bring
128 together information captured in electronic health records (EHRs), and information provided
129 by patients themselves (i.e. from questionnaires and during office visits). This will be achieved
130 using standardized data collection, guided by COPD clinicians both in primary and specialist
131 care. Further, the registry may identify patterns of healthcare before a diagnosis,[16]and has
132 the potential to identify new COPD phenotypes.
133
134 The aim of the Delphi exercise described in this article was to gain expert consensus on a
135 standardized list of variables on demographic, disease monitoring and treatment variables to
136 establish the APEX COPD registry. Selection of these variables was dictated not only by clinical
137 relevance; it was also important that variables were already known to family physicians and
138 that it was practical and feasible to collect them in primary care.
139
140

Methods

Design

This study used a modified, three-round Delphi process to achieve consensus on the core variables to be collected in the APEX COPD registry.[17] Variables were initially selected from relevant COPD guidelines and recommendations to give all potentially clinically relevant options, and subsequently refined by the panel to the items desired for inclusion in the registry.

Panel selection

The APEX COPD Delphi panel consisted of appropriately qualified and experienced individuals in the field of COPD and primary care, capable of providing critical and informed input. This panel included 14 experts in primary and specialist care from the US and internationally – five family physicians, three pulmonologists, six respiratory researchers (five of whom had substantial prior experience as family physicians), with >70% of panel members based in the U.S. **(Table E1)**. The panel members met two or more of the following criteria:

1. Evidence of relevant COPD research published in high-ranking peer-reviewed journals (e.g. high number of citations and research items).
2. A history of participation in the development and/or management of one or more respiratory registries or cohorts, epidemiological databases, and scientific congress committees in a country and/or internationally.
3. Experience as a medical clinician (e.g. physician or nurse) with an interest in advancing COPD management in clinical practice.

Modified Delphi process

A modified Delphi process was used to reach consensus on which data to collect into the registry from EHR, patient reported information/patient reported outcomes (PRI/PROs), and at consultation.[18]The process consisted of three iterative rounds (Round 1 (R1), Round 2 (R2) and Round 3 (R3); **Figure 1**).

Each Delphi panel member was issued an electronic APEX COPD Excel workbook to review, provide suggestions and vote, in order to select core variables. Members then returned the completed Delphi workbooks to the APEX COPD administrator within a four-week time period. The Delphi administrator directly corresponded with all panel members individually to ensure anonymity of replies and was responsible for disseminating workbooks and result summaries for each round.

Delphi Round 1

The Delphi workbook (APEX COPD Workbook Round 1) was developed initially by consolidating variables from current guidelines and recommendations: the American Thoracic Society (ATS) and European Respiratory Society (ERS) joint guidelines, COPD Foundation, and GOLD.[18-25] Variables under consideration included:

- Patient demographics.
- Medical history, symptoms (COPD-relevant), prior exacerbations, exposure, and comorbidities.
- COPD treatment and management, including medications and side effects (such as those related to steroid exposure and/or biologics), adherence data when available,

vaccinations, referrals, surgery, rehabilitation, smoking cessation, and other non-pharmacological strategies.

- Patient-reported information and outcomes including health status scores (COPD Assessment Test (CAT), modified Medical Research Council (mMRC) dyspnea scale), and questionnaires (e.g. inhaler satisfaction questionnaire, and Test of Adherence to Inhalers (TAI)) to measure respiratory inhaler device satisfaction and inhaler adherence.
- Medical test/investigations, including spirometry, electrocardiogram, and biomarkers (blood eosinophils, IgE, and fractional exhaled nitric oxide (FeNO) where possible).

The workbook comprised a two-tab Excel spreadsheet:

- On tab one, displaying the potential core list (**Table 1**), panel members were required to select an option ("Yes" or "No") via a drop-down menu for each variable, indicating whether or not they concurred that the variable would be part of the APEX COPD registry core variable list.
- On tab two, panel members were encouraged to nominate variables from the "additional" variable list (**Table 2**) and/or propose new variables ("Suggested"). During this round, experts were also encouraged to provide comments for excluding or including variables.

At round closure, the Delphi administrator anonymized all returned workbooks and compiled all replies to tabulate frequency of responses, "Yes" and "No," for each variable on the lists. Variable consensus was evaluated using summary statistics (frequency counts) generated with the Microsoft Excel V16.27 statistical package. Delphi R1 consensus rules for each variable assessed by the panel were as follows: Keep (>66% 'yes'); undecided (≥50 to ≤66% 'yes'); exclude (<50% 'yes').

Delphi Round two

All variables from R1 as well as "suggested" variables were included in a single tab in the R2 workbook and the expert panel was requested to engage in a similar voting process for Delphi R2. The Delphi R1 summary results and panel member comments ("Comments") were anonymized and provided in the R2 workbook to facilitate an informed decision. Delphi R2 was divided into 2 parts:

- Round 2a: Each variable that received a 66% or more consensus from the Delphi panel in R2 was moved to a second phase of analysis (R2b). Other variables were excluded from the APEX COPD registry core variable list.
- Round 2b: Variables moved to R2b were analyzed more specifically to determine which data sources they should be collected from (EHR, PRI/PRO, or at the doctor's office (i.e. point of care (PoC))).

Delphi R2 consensus rules for each variable assessed by the panel were as follows: Keep (≥66% consensus); undecided (40 to 65% consensus); exclude (<40% consensus). Additionally, all excluded variables from R2 were vetted by the APEX COPD Operational Management Group (AOMG; **Table E2**). If excluded variables were considered key to COPD primary care by the AOMG, they were re-included for review in R3.

Delphi Round three

The Delphi panel also took part in a similar voting process for Delphi R3 via a third electronically distributed workbook (The APEX COPD Delphi Workbook Round three). The Delphi R2 summary results and panel member comments ("Comments") were anonymized and provided in the R3 workbook to facilitate an informed decision. R2 "Undecided" and additional AOMG vetted variables were included in the R3 workbook. Delphi R3 consensus

rules for each variable assessed by the panel were as follows: keep (≥66% consensus); undecided (40 to 65% consensus); exclude (<40% consensus). All undecided and excluded variables from R3 were vetted by the AOMG. If these variables were considered key to COPD primary care by the AOMG, they were included in the final core variable list.

Results

Delphi Round one

In R1, the expert panel voted on 189 clinical COPD variables belonging to the categories of demographics, disease monitoring, and treatment (**Table E3**). Overall, 149 of the variables received >66% consensus to keep, 25 were undecided (50% to 66% consensus), and 15 were recommended to exclude (receiving <50% consensus) (**Table E4**). All 189 variables were entered into voting round two. Six "suggested" variables recommended by the panel were also added bringing the total to 195 variables to proceed to R2.

Delphi Round two

After voting R2, 25 of the 195 variables were excluded from collection into the registry and 170 were confirmed for collection (**Table E5, Part A**). Of the 170 confirmed variables the Delphi panel recommended that 115 be collected from EHR, and 16 via PRI/PRO. At this stage, no variables were confirmed for collection by clinicians during a visit. (**Table E5, Part B**). Undecided variables were entered into Delphi Round 3. Four undecided PRI/PRO variables from R2a were re-included for review in R3. These were:

- *Poor appetite:* an important factor used in conjunction with other cancer indicators which received consensus votes to be included for collection.
- *Easy bruising:* specific types of physiological side effects were not specified for voting; bruising is a common and important side effect to assess in patients receiving inhaled corticosteroid (ICS).
- *Pain (headache and muscle):* specific types of pain as side effects were not specified for voting; muscle pain and headaches are common and preventable effects to assess in patients receiving inhaled medications.

- *Low birth weight:* an important childhood risk factor which may not be recorded in patients' EHR.

One excluded PoC variable from R2a was re-included for review in R3. This was:

- *Inhaler technique assessment:* important for interpretation of peak inspiratory flow rate (PIFR) which received a consensus vote to be included for collection from the EHR and an undecided vote to be collected during the office visit.

Delphi Round three

A final round of voting (R3) was undertaken to vote on 'undecided' PRI/PRO and PoC variables from R2. A total of 13 PRI/PRO and two PoC variables were kept on consensus. Of the remaining 27 undecided PRI/PRO variables at R3, three were confirmed for collection by the AOMG (**Table E6**). The reasons were:

- *Pulmonary rehabilitation:* critical for prevention of disease progression and management
- *Influenza vaccine:* can be administered by an external provider and therefore may not be collected in patients' EHR. This information is critical for informing preventative care.
- *Oral treatment side effect (candidiasis):* specific types of oral side effects not specified for voting; oral candidiasis is a common and important side effect to assess in patients receiving ICS.

Two additional PRI/PRO variables excluded in R2b were vetted and included in the final core variable list. These were:

- *Asthma diagnosis (age of onset):* decision to collect via PRI/PRO in addition to EHR to identify age of onset where this information is unavailable in EHR.

- *Physiological treatment side effect (easy bruising):* specific types of physiological side effects were not specified for voting; bruising is a common and important side effect to assess in patients receiving ICS.

Of the three undecided variables for collection during the office visit at R3, three were confirmed for collection by the AOMG. These were:

- Number of severe exacerbations in the past year,
- Forced expiratory volume in one second (FEV_1) post-bronchodilator, and
- Forced vital capacity (FVC) post-bronchodilator

These were all considered critical for COPD management and will be collected at PoC only if missing from EHR and PRI/PRO.

The core variables that achieved consensus via the closely guided three rounds of Delphi were included in the final core variable list (**Table 3**).

Discussion

Using the knowledge and experience of an international panel of COPD experts, workable criteria for registry purposes, a standardized core set of variables, and a potential method to unify data for COPD in the U.S. were generated and agreed to by consensus. All potential variables underwent a rigorous, stepwise consensus process to ensure the collection of the minimum required information to effectively and practically study the diagnosis and management of patients with COPD. Of the initially circulated “potential core” and “suggest” variables circulated, up to 115 were selected from existing EHR for integration in the APEX COPD registry, 34 PRI/PRO variables and five variables to be collected during office visits. These selected variables fall into three broad categories (i.e. demographics, disease monitoring, and treatment), and should include information on diagnosis, exacerbations, symptoms, lung function, and quality of life, co-morbidities, smoking history, treatment specifics (including side effects), inhaler management (including inhaler technique) and education/self-management. They have been selected not only due to their clinical relevance and usefulness to family doctors and patients (**Table 3**) but also with feasibility, familiarity and practicality of collection in mind. This will ensure that the APEX COPD registry will be an asset to family doctors; a tool to identify how patients with COPD are managed in real life, in a population rarely included in randomized controlled trials Following ratification of data collection, the registry plans to integrate information from multiple sources with maximal efficiency and present it to clinicians and patients in a structured and clinically useful format, with the aim of improving primary care for patients diagnosed with COPD. Data from the registry will also be used to answer key research questions relating to COPD in primary care, facilitating insight into this prevalent chronic disease. The outcomes of such research and any

new research proposals will be continuously updated via the APEX COPD website (https://www.apexcopd.org/).

The panel-approved APEX COPD registry variables were chosen to ensure a comprehensive description of patients diagnosed with COPD and managed in real-life clinical practice among family physicians in the U.S. Collection of baseline information on diagnosis, infection, exacerbations, severity classification, health status, and treatment-/co-morbidity-patterns will provide a snapshot of clinical phenotypes of COPD, a better understanding of how patients are diagnosed and managed in primary care (e.g. use of spirometry), an estimation of the burden of disease (including the corticosteroid burden), and an assessment of whether diagnoses and severity classifications are correct and treatment is appropriate (compared to guideline recommendations).[8] Appropriate variables will be assessed longitudinally to examine their impact on disease progression and treatment outcomes. For example, data may be assessed to (i) compare the clinical, safety and cost-effectiveness of current COPD treatments, (ii) describe treatment changes over time (and the reasons for those changes), (iii) assess the impact of inhaler technique and inhaler type on key outcomes, (iv) analyze risk factors associated with disease progression and healthcare utilization and (iv) predict response to treatment (e.g. biomarkers).

As well as the collection of key COPD variables from multiple sources, the APEX COPD registry has numerous other assets, including (i) its size and scope, (ii) innovative use of technology to collect high quality data, (iii) inclusion of clinical and database management expertise, (iv) inclusion of expertise on gathering patient reported information (v) an integrated communication strategy and (vi) the organizational structure to oversee the initiative and ensure its continuance. Currently, it is planned to capture information from 3,000+ patients

diagnosed with COPD, with a wide geographic coverage throughout the U.S, benefiting from both scale and generalizability to the wider COPD population. Patients included will have a diagnostic, monitoring, or review code for COPD prior to or at consultation and be aged ≥35 years at COPD diagnosis. Data collected by APEX COPD registry will be maintained as a limited dataset in the APEX COPD database. Data will be completely de-identified, at the individual level, and anonymized when providing subsets of data for research purposes. Electronic data capture (EDC) systems will be utilized to capture data directly from EHR, which may already include valuable information on symptoms, lung function, COPD staging, pharmacologic treatment, co-morbidities, and exacerbations. Use of an existing data resource to populate the APEX COPD registry precludes the need for lengthy additional data collection at the PoC, which will improve efficiency, reduce workload, time, and cost, and enhance the quality of data collected.

Expertise is embedded into the initiative, including the panel of 14 COPD experts on the APEX COPD Steering Committee, recruitment of primary care consultants experienced in COPD management, incorporation of a dedicated communications team to disseminate key research findings and partnership with experts in PRI and PRO (COPD Foundation and the American Academy of Family Physicians), and database management and registry delivery (DARTNet Institute, CO, US). Communication of APEX COPD registry research findings will also be facilitated via regular publication in peer-reviewed journals and dissemination of findings at international and regional scientific meetings. The APEX COPD registry is overseen by five bodies (OPC Global, The Respiratory Effectiveness Group, the Anonymized Data Ethics & Protocol Transparency Committee, the American Academy of Family Physicians, and the APEX COPD Steering Committee) safeguarding continuance of the registry into the future, and

ensuring APEX COPD research is ethical, clinically appropriate and continues to bring genuine value to physicians who manage COPD in real-life clinical practice, and to patients who live with COPD.

Strengths and weaknesses

Fourteen Delphi panel members from four countries (>70% US-based experts) participated in one or more Delphi rounds, to allow for broad consensus to be obtained, and to ensure recommendations were pertinent not only to the U.S., but also maintained applicability beyond U.S. borders. This approach dilutes the opinion of a single expert, so bias is decreased and diversity within the expert panel is maximized. Panel members were chosen for their expertise in the research field, and relevant medical practice and experience. The anonymity of the survey ensured all opinions were given equal weight and consideration. The Delphi process was carried out online, to facilitate ease of yes/no voting for each variable, as well as rapid and accurate vote counting and classification (i.e. yes, no, undecided) at the end of each Round. It also facilitated rapid and open communication among the COPD experts. The results covered a wide range of areas where consensus was achieved. Although the study employed a relatively small Delphi panel, recent studies have found that reliable outcomes can be obtained with a relatively small number of Delphi experts.[27] The Delphi panel was also not fully representative of the diversity of stakeholders involved in respiratory care at the primary care level. In particular, the opinions of payers and patients were not solicited. Another limitation of the study is that the response rate was not 100%; a total of 13 of 14 experts (93%) responded to all three Delphi rounds. However, there was consistency in the number of experts who participated in each round (R1 = 93%; R2 = 100%; R3 = 100%), which ensured that the possibility of reaching consensus was conserved.

In conclusion, COPD experts have agreed on core variables to collect in the APEX COPD registry. The majority of these variables will be extracted from EHRs but will also include PRI/PRO and PoC data from 3,000+ patients diagnosed with COPD across the U.S. Data will be integrated, standardized and stored in the APEX COPD database and made available for COPD-related research. It will be used to analyze COPD natural history as well as clinical, safety and cost-effectiveness of current COPD treatments in primary care across the US.

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Declaration of Interest

Chelsea Edwards is an employee of the company Optimum Patient Care, which is a co-founder of the APEX COPD initiative.

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Maja Kruszyk is an employee of the company Optimum Patient Care, which is a co-founder of the APEX COPD initiative.

Chantal Le Lievre is an employee of the company Optimum Patient Care, which is a co-founder of the APEX COPD initiative.

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581 **Legend to figures**

582 Figure 1: General flow of the APEX COPD Registry Delphi process

583 Figure 2: Summary of the Delphi results for the APEX COPD registry

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585 **Figure 1**

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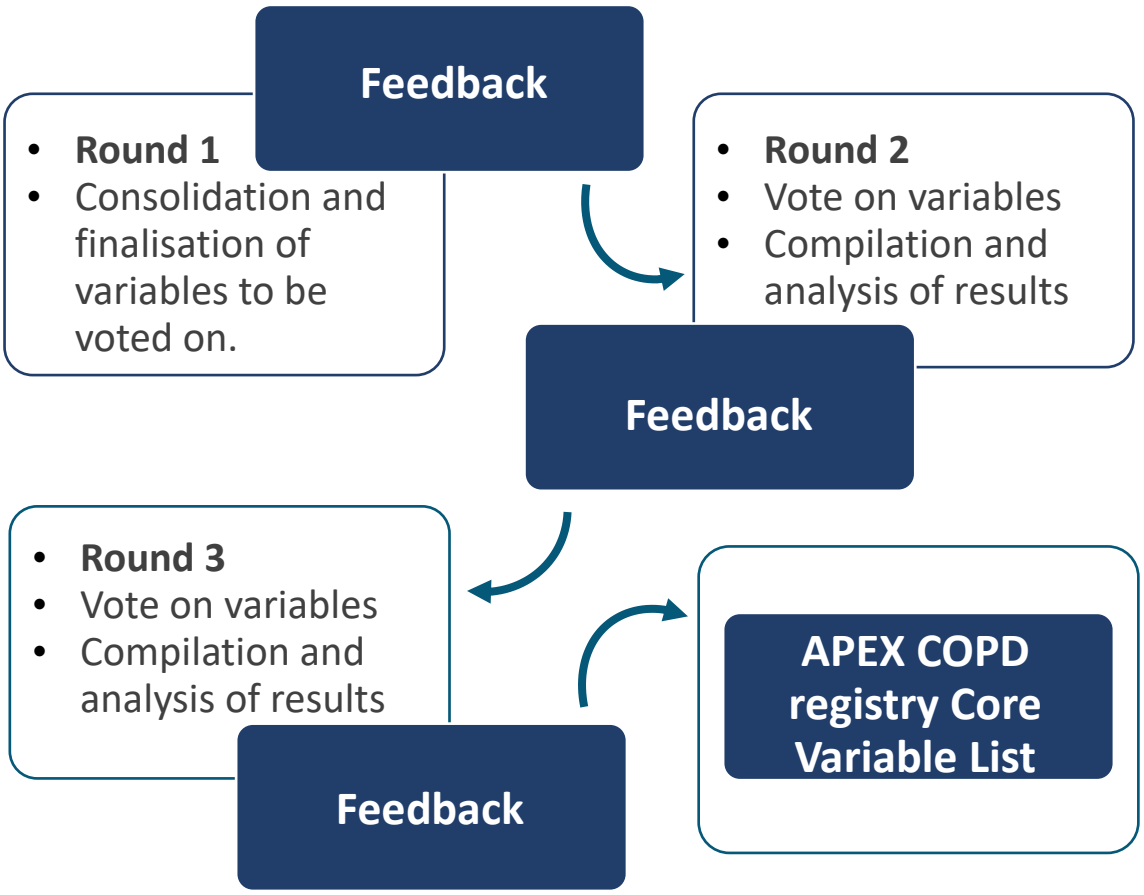
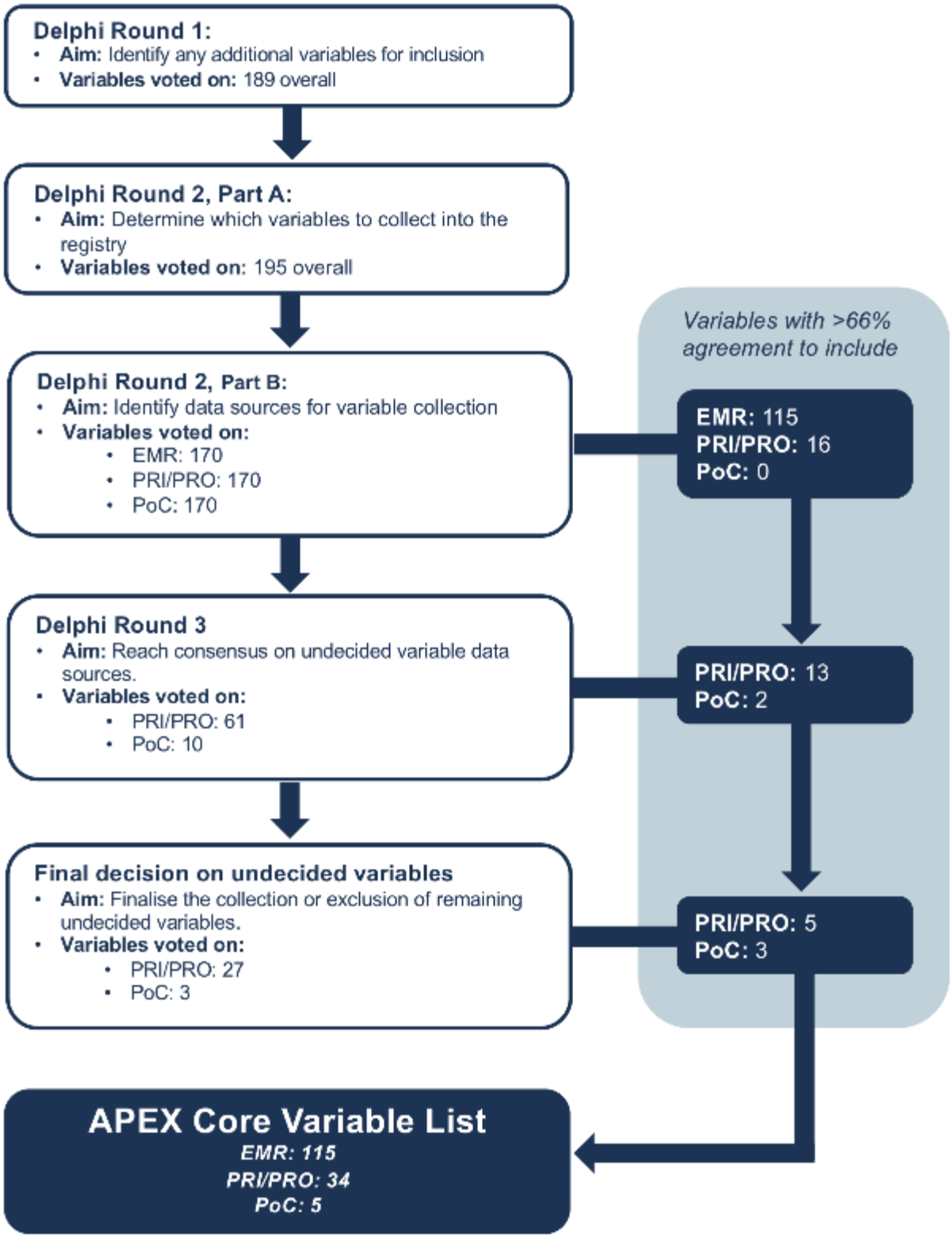


590 **Figure 2**



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593 **Table 1.** Sample of the 'Potential Core' variable list from the APEX COPD Registry Delphi workbook Round 1

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Should this variable be included? (please select yes/no from drop-down menu in each cell)	Please provide any comments regarding exclusion/modification	Category	Variable	Variable inclusion in prominent COPD templates and guidelines					Entry format	Response options	Template auto populated by:		Entered at initial consult	Entered annually
				GOLD 2018	ERS/ATS 2004, 2007, 2011, 2017	COPD Foundation Guide 2013	OPC UK (template and PRO)	COPDX 2018 (Australia)			Electronic Health Record (EHR)	Patient questionnaire		
		Demographics	Height (In)	✓	✓	✓	✓	✓	Numeric	Numeric	✓		✓	✓
			Weight (Lb)	✓	✓		✓	✓	Numeric	Numeric	✓		✓	✓
			Biological sex	✓	✓	✓	✓	✓	Drop-down	Male/Female	✓		✓	
			Age (Yrs)	✓	✓	✓	✓	✓	Numeric	Numeric	✓		✓	
		Physiological measurements	Predicted FEV1 (Autocalculated)	✓			✓	✓	Autocalculated	Numeric	✓		✓	✓
			FEV1 pre-bronchodilator	✓			✓	✓	Numeric	Numeric	✓		✓	✓
			FEV1 post-bronchodilator	✓	✓	✓	✓	✓	Numeric	Numeric	✓		✓	✓
			FEV1 (pre-bronchodilator)/Predicted FEV1 (Autocalculated)	✓			✓	✓	Autocalculated	Numeric	✓		✓	✓

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601 **Table 2.** Sample of the 'Additional' variable list from the APEX COPD Registry Delphi workbook Round 1

Should this variable be included? (please select yes/no from drop-down menu in each cell)	Please provide any comments regarding exclusion/modification	Variable	Variable inclusion in prominent COPD templates and guidelines					Entry Format	Reponse options	Template autopopulated by:		Entered at initial consult	Entered annually
			GOLD 2018	ERS/ATS 2004, 2007, 2011, 2017	COPD Foundation Guide 2013	OPC UK (template and PRO)	COPDX 2018 (Australia)			Electronic Health Record (EHR)	Patient questionannaire		
		Disease monitoring											
		Symptoms											
		Wheezing	✔	✔			✔	Check box	Yes	✔		✔	✔
		Persistent cough	✔	✔	✔	✔	✔	Check box	Yes		✔	✔	✔
		Productive cough	✔	✔	✔	✔	✔	Check box	Yes		✔	✔	✔
		Breathlessness	✔	✔		✔	✔	Check box	Yes		✔	✔	✔
		Chest tightness	✔			✔	✔	Check box	Yes		✔	✔	✔
		Cyanosis					✔	Check box	Yes	✔		✔	✔
		Sputum purulence	✔	✔				Check box	Yes	✔		✔	✔
		Fatigue	✔					Check box	Yes	✔	✔	✔	✔
		Breathlessness / quality of life											
		Modified Medical Research Council Dysponea Scale **Which statement best describes you?**	✔	✔	✔	✔	✔	Radio button	Not troubled by breathlessness (except on strenuous exercise) Short of breath when hurrying or walking up a slight hill Slower in walking than others of the same age on level ground because of breathlessness, or have to stop for breath when walking at your own pace. Stopping for breathe after about 100 m or after a few minutes on level ground. Too breathless to leave the house, or when dressing/undressing.		✔	✔	✔

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604 **Table 3.** Final core variable list to be collected from A) the electronic health record (EHR), B) patient reported information and outcomes, and

605 C) at the point of care

Category*	Sub-category	Variable	Why is it important to collect?
EHR variables (n=115)			
Demographics		Height (In)	• Required to predict lung function parameters. • Women and some ethnicities have smaller lungs, so these data could prospectively show risk of COPD at different smoking rates etc.
		Weight (lb)	
		Biological sex	
		Age (yrs)	
		BMI	
		Race	
Disease monitoring	*COPD diagnosis*	COPD	• These are different phenotypes of COPD and when available should be captured separately
		Chronic bronchitis	
		Emphysema	
		AATD	
	Differential diagnosis	Asthma	• Asthma is the most common differential diagnosis and often co-exists with COPD (i.e. ACOS) • GOLD recommendation to identify and appropriately manage.[8]
	Respiratory infection	Number pneumonia infections in past 2 yrs	• May be indicators of unrecognized COPD exacerbations • May be side effect of ICS used in COPD management
		Number of other RTI in past 2 yrs	
	Exacerbations	No. moderate exacerbations in past year (also indicated by short course of Atb or OCS	• Necessary to characterize severity, assess treatment effectiveness and monitor disease progression • May indicate a need for treatment escalation or treatment switch if the disease is poorly controlled.[8]
		No. severe exacerbations in past year (also indicated by hospitalization and course of Atb/OCS)	
	Symptoms	Wheezing	• The most common symptom of COPD, after dyspnea
	Physiological measurements	Predicted FEV_1 (auto-calculated)	• FEV_1/FVC post bronchodilator necessary for COPD diagnosis
		FEV_1 pre-bronchodilator	

Category*	Sub-category	Variable	Why is it important to collect?
Disease Monitoring (cont')		FEV_1 post-bronchodilator	• FEV_1 provides information on severity of lung function impairment • Reversibility indicates the possibility of co-morbid asthma • FVC indicates restrictive issues • Oxygenation falls later in the disease. But treating with O_2 is the only medication that affects prognosis • Blood eosinophilia a useful predictor of ICS response • CXR: useful for comorbidity assessment • CT: necessary for bronchiectasis and lung cancer screening • CV disease (and BP) is the major comorbidity
		FEV_1 (pre-bronchodilator)/Predicted FEV_1 (auto-calculated)	
		Predicted FVC (auto-calculated)	
		FVC pre-bronchodilator	
		FVC post-bronchodilator	
		FVC (pre-bronchodilator)/Predicted FVC (auto-calculated)	
		Predicted FEV_1/FVC ratio (auto-calculated)	
		FEV_1/FVC pre-bronchodilator (auto-calculated)	
		FEV_1/FVC post-bronchodilator (auto-calculated)	
		Reversibility (%)	
		PIFR	
		Pulse oximetry (spO_2, %)	
		Full blood count	
		Blood eosinophil count	
		Chest X-ray	
		CT scan	
		Systolic BP (mm Hg)	
		Diastolic BP (mm Hg)	
		6-minute walking test (ft)	
	GOLD categorization	GOLD 1-4 (auto-calculated)	• To assess appropriateness of severity classification and its impact on disease & treatment outcomes
		GOLD A-D (auto-calculated)	
	Differential diagnosis (predicting asthma)	Allergy	• Comorbidities most likely associated with asthma • Sinusitis is related to infectious risk
		Rhinitis	
		Nasal polyps	
		Eczema	
		Sinusitis	
		Ankle edema	

Category*	Sub-category	Variable	Why is it important to collect?
	Differential diagnosis (predicting heart failure)	Echo cardiogram	• Signs of left and or right heart failure
		Elevated B-type natriuretic peptide	
	Differential diagnosis (predicting lung cancer)	Weight loss	• TB differential diagnosis
		Hemoptysis	
	Other diff. diagnosis	Pneumonia	• A serious co-morbidity to COPD • A potential side effect of ICS use in COPD management
	Co-morbidities (cardiovascular)	Angina pectoris/Heart disease/CHD	• May require further evaluation/investigation • May affect outcomes • CHF also presents with dyspnea and is not always easy to tell apart • May significantly impact quality of life
		Heart failure	
		Stroke	
		Hypertensive disease	
	Co-morbidities (pulmonary)	Lung cancer	
		Obstructive sleep apnea	
		Hypoxemia	
	Co-morbidities (endocrinological)	Diabetes mellitus	
		Osteoporosis	
		Osteoarthritis	
		Metabolic syndrome	
	Co-morbidities (mental)	Depression	
		Anxiety	
	Co-morbidities (other)	GERD	
		Anemia	
Treatment & management	*Bronchodilators*	SABA	Required to: • Characterize treatments used • Assess frequency of use
		LABA	
		SAMA	
		LAMA	

Category*	Sub-category	Variable	Why is it important to collect?
Treatment & management (cont')	*Steroids*	ICS	• Assess appropriateness of treatment selection • Assess effectiveness of treatments and regimens (e.g. dual vs triple) • Assess ICS over use • Assess OCS burden • Assess impact of inhaler choice
		OCS	
	Combinations	SABA/SAMA	
		LABA/LAMA	
		ICS/LAMA	
		ICS/LABA	
		ICS/LAMA/LABA	
	Co-morbidity treatments	Heart failure	• To assess their impact on prognosis
		Diabetes	
		Osteoporosis	
		Asthma	
	Other treatments	Antibiotics	• To evaluate effectiveness and exacerbation risk reduction
		Macrolides	
		PDE inhibitors	
		Methylxanthines (e.g. theophylline)	
		LTRA	
		Diuretics	
		Mucolytics	
	Smoking (cigarettes)	Smoking status	• The most common etiology
		How many years has patient smoked?	
		Pack years	
	Vaccinations	Influenza	• Key preventative vaccinations. Decrease the risk of LTRI.[8]
		Pneumococcal (both)	
	Smoking cessation	Smoking cessation advice given	• To assess prognosis & determine which works best • Has the greatest capacity to influence the natural history of COPD. GOLD recommends to collect in order to monitor and encourage appropriate cessation interventions.[8]
		Referral to stop-smoking clinic/advisor	
		Nicotine replacement therapy	
		Drug therapy (e.g. Bupropion)	
	Surgery	Bullectomy	
		Lung Volume Reduction Surgery (LVRS)	

Category*	Sub-category	Variable	Why is it important to collect?
		Lung volume reduction coil	• To identify best candidates and outcome for each of these surgical interventions
		Endobronchial Valve (EBV)	
		Lung transplant	
		Chest wall vibration	
	Specialist referral	Palliative care	• To consider respiratory evaluations by non-respiratory or primary care doctors
		Physiotherapist	
		Occupational therapist	
		Speech therapist	
		Clinical psychiatrist	
		Clinical psychologist	
		Dietitian	
		Exercise physiologist	
		Chest physician	
	Other therapies	Pulmonary rehabilitation (PR)	• To assess availability and efficacy • PR is critically important for best outcomes
		Oxygen therapy	
		Home nebulizer	
		Ventilatory support	
PRI/PRO variables (n=34)			
Disease monitoring	*Differential diagnosis*	Asthma	• Asthma is the most common differential diagnosis and often co-exists with COPD (i.e. ACOS) • GOLD recommendation to identify and manage appropriately.[8]
	Respiratory infections	No. of pneumonia infections in past 2 yrs	• Effect on disease outcome • Effect on treatment outcome
		No. of other RTI in past 2 yrs	
	Exacerbations	No. of moderate exacerbations in past year (also indicated by course of Atb/OCS)	• Key patient outcome • Indicator of severity, disease progression and effectiveness of treatment

Category*	Sub-category	Variable	Why is it important to collect?
Disease Monitoring (cont')		No. of severe exacerbations in past year (also indicated by emergency hospitalization and course of Atb/OCS)	• Indication of a need for treatment escalation or treatment switch.[8]
	Health status (QoL)	Modified MRC Dyspnea Scale COPD Assessment Test	• Key patient outcome (validated scales) • Indicator of severity, disease progression and effectiveness of treatment.[28]
	Risk factors	Childhood respiratory infections Occupational exposure Tobacco exposure Age of onset of respiratory symptoms yrs Family history of COPD	• Little- and well-known risk factors for COPD development • History of severe childhood respiratory infection has been associated with reduced lung function & increased respiratory symptoms in adulthood.[29]
	Co-morbidities (mental)	Depression Anxiety	• Prognostic outcomes and indicators of QoL
Treatment & management	*Inhaler management*	Spacer with MDI Inhaler technique training Inhaler use/adherence Test of Adherence to Inhalers (TAI) questionnaire Inhaler satisfaction questionnaire	• Good inhaler technique is critical to get medication where it is needed. • Poor technique and poor adherence are commonly associated with poor symptom control in COPD.[30] • Patient satisfaction & preference are often not collected. Patient satisfaction with treatment may influence adherence.[22,31]
	Treatment side effects	Oral Physiological	• An important patient outcome which may impact treatment adherence and continuance
	Smoking	Smoking status Date ceased smoking (if applicable) How many cigarettes smoked per day? How many years has patient smoked? Uses e-cigarette?	• Important for prognosis

Category*	Sub-category	Variable	Why is it important to collect?
Treatment & managment (cont')	*Vaccinations*	Influenza	• A preventable issue
	Smoking cessation	Desire to quit smoking Tried to quit in the past Smoking cessation advice given	• To assess motivation to quit • To encourage motivational interviewing
	Education & self-management	COPD education COPD self-management plan Patient's use of COPD self-management plan	• To assess available, utility and the benefits (if any) of action plans • Education & self-management interventions can help improve the physical & psychological condition of COPD patients & promote long-term adherence to health-enhancing behaviors.[32]
	Other therapies	Pulmonary rehabilitation	• To assess availability and efficacy • PR is critically important for best outcomes
PoC Variables (n=5)			
Disease monitoring	Exacerbations	No. of moderate exacerbations in past year (also indicated by course of Atb/OCS) No. severe exacerbations in past year (also indicated by emergency hospitalization and course of Atb/OCS)	• Key patient outcome • An indicator of severity, disease progression and effectiveness of treatment
	Physiological measures	FEV_1 post-bronchodilator FVC post-bronchodilator	• An indicator of illness progression • To unmask other illnesses
Treatment & management	Inhaler management	Inhaler technique assessment	• To assess impact on treatment efficacy and to better select device if treatment or device change required. This might include observed technique and PIFR assessment if felt clinically necessary

AATD: Alpha-1 antitrypsin deficiency; Atb: antibiotic; BMI: body mass index; BP: blood pressure; CHD: coronary heart disease; COPD: Chronic Obstructive Pulmonary Disease; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GERD; gastroesophageal reflux disease; GOLD: Global initiative for chronic Obstructive Lung Disease; ICS: inhaled corticosteroid; LABA: long-acting β_2-agoinist; LAMA: long-acting muscarinic antagonist; LTRA:

Category*	Sub-category	Variable	Why is it important to collect?
leukotriene receptor antagonist; MDI: metered dose inhaler; MRC: Medical Research Council; OCS: oral corticosteroid; PDE: phosphodiesterase; PIFR: peak inspiratory flow rate; RTI: respiratory tract infection; SABA: short-acting β_2-agonist; SAMA: short-acting muscarinic antagonist			

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607 *Variables are categorized in this way to simplify Delphi voting. For the purpose of reporting variables may fall into multiple categories

Online repository

Supplementary Table E1. Delphi panel members

Member	**Primary area(s) of expertise**	**Country**
Alvaro Aranda	Specialist	Puerto Rico
Ku-Lang Chang	Primary care	USA
Chester Fox	Primary care	USA
Gokul Gopalan	Research	USA
MeiLan Han	Specialist	USA
Alan Kaplan	Primary care, specialist	Canada
Janwillem Kocks	Research, primary care	Netherlands
Catherine Mahle	Research	USA
Barry Make	Specialist	USA
Wilson Pace	Research, primary care	USA
David Price	Research, primary care	UK/Singapore
Neil Skolnik	Primary care	USA
Barbara Yawn	Research, primary care	USA

Supplementary Table E2 APEX COPD registry Operational Management Group

Member	
Victoria Carter	Operational lead
Chelsea Edwards	Research lead
Gokul Gopalan	Steering committee member
Janwillem Kocks	Steering committee member
Wilson Pace	Steering committee member
David Price	Steering committee member
Barbara Yawn	Steering committee member

Supplementary Table E3. Categorization of potential APEX COPD registry variables

Category	Number of variables listed
Demographics	6
Disease monitoring	
COPD diagnosis	4
Differential diagnosis	1
Respiratory infections	2
Exacerbations	2
Symptoms	8
Health status (quality of life)	3
Physiological measurements	32
GOLD categorization	2
Risk factors	13
Differential diagnoses	22
Co-morbidities	17
Treatment	
Bronchodilators	4
Steroids	2
Combinations	5
Inhaler management	5
Co-morbidity treatments	4
Other treatments	8
Treatment side effects	9
Smoking	5
Vaccinations	2
Smoking cessation	7
Education & self-management	6
Surgery	6
Specialist referral	10
Other therapies	4
Total	**189**

Supplementary Table E4. Delphi Round 1 results summary

R1 variable summary	Number	Consensus criteria	Remarks
Potential variables			
Total number of variables	189		
Consensus to keep	149	>66%	All variables entered in R2 with additional recommendations.
Undecided	25	50-66%	
Recommendation to exclude	15	<50%	
Recommendation to add	6		

Supplementary Table E5. Delphi Round 2 results summary

R2 variable summary	Number	Consensus criteria	Remarks
All potential variables			
Part A: Keep, undecided or exclude			
Total number of variables	195		
Consensus to keep	170	≥66%	Included in final core variable list *if consensus was reached for collection by EHR, patient reported information outcomes, or at the point of care.*
Undecided	20	40-65%	Included in R3 at the discretion of the Operational Management Group*
Consensus to exclude	5	<40%	Excluded from final core variable list
Part B: from which data source – EHR, PRI/PRO or PoC?			
Potential variables for collection from EHR			
Total number of variables	170		
Consensus to keep	115	≥66%	Included in final core variable list
Undecided	48	40-65%	Entered into R3
Consensus to exclude	7	<40%	Excluded from final core variable list
Potential variables for collection as patient reported and information and outcomes			
Total number of variables	170		
Consensus to keep	16	≥66%	Included in final core variable list
Undecided	57	40-65%	Entered in R3
Consensus to exclude	97	<40%	Excluded from final core variable list
Potential variables for collection at the point of care			
Total number of variables	170		
Consensus to keep	0	≥66%	Included in final core variable list
Undecided	9	40-65%	Entered in R3
Consensus to exclude	161	<40%	Excluded from final core variable list**

*4 undecided variables were included in R3 for collection as patient reported information and outcomes, remaining variables were excluded from the final core variable list.

With the exception of one variable, included in R3 at the discretion of the APEX COPD registry Operational Management Group (Table E2**).

Supplementary Table E6. Delphi Round 3 results summary

R3 variable summary	Number	Consensus criteria	Remarks
Remain potential variables for collection as patient reported and information and outcomes			
Total number of variables	61		
Consensus to keep	13	≥66%	Included in the final core variable list
Undecided	27	40-65%	Included in the final core variable list at the discretion of the Operational Management Group*
Consensus to exclude	21	<40%	Excluded from final core variable list
Remaining potential variables for collection at the point of care			
Total number of variables	10		
Consensus to keep	2	≥66%	Included in the final core variable list
Undecided	3	40-65%	Included in the final core variable list at the discretion of the Operational Management Group**
Consensus to exclude	5	<40%	Excluded from final core variable list

*4 undecided variables were included the final core variable list.

**All undecided variables were included the final core variable list.