Respiratory Effectiveness Group

REG STUDY PROTOCOL

LONG TITLE:

EVALUATION OF COPD CONTROL AND ITS CLINICAL IMPLICATIONS IN A REAL-LIFE UK PRIMARY CARE POPULATION

SHORT TITLE:

VALIDATION OF COPD CONTROL: UK PILOT

Research Protocol developed by The Respiratory Effectiveness Group

CONTENTS PAGE

BACKGROUND & RATIONALE

Chronic obstructive pulmonary disease (COPD) is a broadly heterogeneous condition. Optimum therapeutic outcomes require treatment to be tailored to the different clinical characteristics and severity of each patient (1-3). To a certain extent, the Spanish Guidelines for COPD (GesEPOC) represent a model of transition towards personalized medicine (4). In these guidelines pharmacological treatment is established with a combination of two essential elements: (i) the determination of the clinical phenotype and (ii) evaluation of the level of severity with the use of a multidimensional index. Multiple therapeutic alternatives emerge from the interaction between these two axes (clinical phenotype and the level of severity), constituting the first step towards individualization of treatment, which has been followed by other national clinical guidelines (5).

However, this approach can overlook changes in the day-to-day activities or symptoms of the patient, changes that may warrant modifications to their existing treatment. Within each clinical phenotype and each level of severity of COPD there are patients with a range of different "expressions" (i.e. symptoms, activity limitations, short-term changes) of their disease. Thus, the concept of disease control may help to better assess the state of the patients and their likely response to treatment. A third axis (control of the disease) should help in therapeutic decision making and has been recently proposed (6,7).

The concept of control has been extensively developed in asthma but little-explored in COPD. Recently, however, Soler-Cataluña et al proposed a new definition/concept of control for COPD. The concept aims to help describe the current clinical "situation" of the patient and to provide a tool that will help guide optimum treatment approaches for patients with COPD(6).

The definition has two components: (i) COPD impact and (ii) COPD stability. "Impact" is a cross-sectional concept that evaluates the clinical status of a patient. It is static assessment corresponding to a specific moment and can be assessed by questionnaires (i.e. the COPD Assessment Test [CAT] or the Clinical COPD Questionnaire [CCQ]) or evaluated based on a patient's degree of dyspnea, use of rescue medication, level of physical activity and sputum colour. The temporal evolution of this impact (i.e. COPD stability) is a dynamic term. "Stability" is a longitudinal concept that requires the absence of exacerbations and deterioration in the aforementioned variables or in CAT or CCQ scores. Hence, control is defined as a condition that has both low impact (adjusted for severity) and stability (6).

Having proposed the concept of control in COPD, it is now important to establish whether the it has clinical validity and utility, specifically in terms of predicting outcomes and guiding on-going COPD management (and/or whether the measure may benefit from further refinement).

A multi-centre prospective trial is planned. In the interim, this study proposes a database pilot validation of the concept, which can then inform (but also be further validated by) the intended prospective study.

AIM & OBJECTIVE

The aims of the proposed study are to:

(i)   Characterise COPD patients treated in UK routine primary care in terms of their COPD control; and to,

(ii)   Evaluate the clinical implications of control status.

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STUDY DESIGN & DATASET

Data source

The **OPCRD** comprises data extracted through the Optimum Patient Care (OPC) Clinical Service Evaluation. The clinical review involves a combined review of (anonymised) electronic medical records (EMRs) and patients' responses to disease-specific questionnaires (see **Appendix 1**) and characterizes patients in terms of their demography, disease control and exacerbation history. The review process produces patient-level reports that makes guideline-based recommendations for possible management changes to optimise control at the lowest possible therapeutic dose and reduce potential future exacerbation risk.

At the time of writing, OPCRD contains anonymised, research-quality data for approximately 2.5 million patients of whom from more than 525 practices across the UK that subscribe to the OPC Clinical Service Evaluation (see **Appendix 2** for OPCRD Data Dictionary). Wihtin the database, there are EMR data available for approximately 135,000 patients, of whom a sugbroup also have linked COPD questionnaires data.
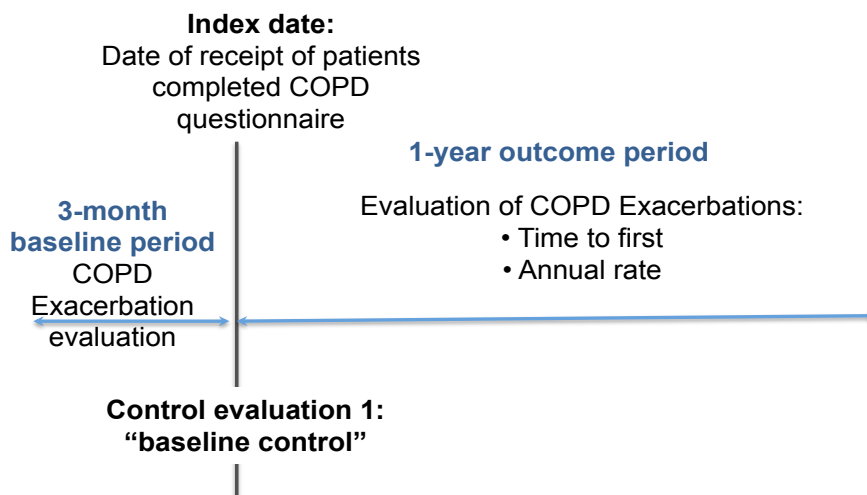
Study Design

This will be a prospectively planned, historical database study on retrospective, electronic medical records and linked COPD questionnaire data from the Optimum Patient Care Research Database (OPCRD).

Study Period

The study will consist of:
- A 3-month baseline period (to inform the baseline control evaluation);
- An index date – the date of receipt of the patients' completed COPD questionnaire
- A 1-year follow-up period, immediately thereafter.

Index date:
Date of receipt of patients completed COPD questionnaire

1-year outcome period

Evaluation of COPD Exacerbations:
- Time to first
- Annual rate

3-month baseline period
COPD Exacerbation evaluation

Control evaluation 1:
"baseline control"

The index date will be linked to date of EMR extraction as questionnaire is issued at time of EMR extraction and routinely completed and returned within 3 months.

As the number of patients within the OCPRD who have completed multiple questionnaires are too small to enable a longitudinal evaluation of control, in the minority of patients with mulitple

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questionnaire records, the index date will be defined as the date of completion of their most recently (i.e. latest) questionnaire.

STUDY POPULATION

Eligibility Criteria

Inclusion criteria

To be eligible for inclusion in the study, patients must meet the following criteria:

- Have a COPD diagnosis:
  - Physician-diagnosed COPD (presence of a COPD Read code); and/or
  - Spirometry-defined COPD: post-bronchodilator FEV1/FVC<0.7
- Aged ≥40 years
- Current or ex-smokers
- Recorded COPD Questionnaire data
- ≥3 months' continuous clinical records immediately prior to the index date
- ≥1 year of continuous clinical records immediately following the index date.

Exclusion criteria

To miniimse the risk of confounding within the dataset, patients with any of the following will be excluded from the analysis:

- Any chronic respiratory condition other than COPD, asthma or bronchiectasis s (e.g. cystic fibrosis, lung fibrosis)
- Patients with potential severe comorbidity at index date, defined as those with a recorded data of death within the 24 months following index date.

OUTCOMES

Co-primary endpoints

The primary endpoint of the study is the difference between patients controlled vs uncontrolled at baseline / index date in terms of:
a) Time to first COPD exacerbation
b) Exacerbation rate over the 1-year outcome period

Outcome definitions

As disease impact varies for different levels of COPD severity, the definition of COPD control differs for different severities of COPD. Patients will be stratified by BODE Index (mild/moderate: ≤4 points; severe/very severe: ≥5 points; see **Appendix 3**) prior to calculation of COPD Control.

COPD Control: will be defined as fulfillment of both the following:
(a) <u>Low impact</u>: according to the severity of the disease, as evaluated at index date (see table below), AND
(b) <u>Disease stability</u>: defined as absence of exacerbations in the last three months.

COPD poor control (or "limited control"): all others

See summary table on p6.

	Mild to moderate severity (BODE/Ex ≤4 points)		Severe/very severe COPD (BODE/Ex ≥5 points)	
	Low impact	High impact	Low impact	High impact
Clinical Evaluation				
Dyspnea (mMRC)	0 – 1	≥ 2	0 - 2	≥3
Rescue medication	≤3 times in the last week	>3 times in the last week	≤2 times a day	>2 times a day
Daily physical activity (time walked/day)	≥60 min	<60 min	≥30min	<30min
Sputum color^	Absent or White	Dark	Absent or white	Dark
Questionnaires of clinical control:				
- CAT	≤10	>10	≤20	>20
- CCQ*	≤1	>1	≤2	>2

^sputum colour is not routinely collected in the OPC COPD questionnaire, but Read codes associated with sputum colour will be used where available. Where not available, the COPD questionnaire question: *"I have no phlegm (mucus) on my chest"* will be used as a proxy:
• Score 0-4: proxy for absent or white
• Score 5–6: proxy for Dark
*CCQ is not currently captured in the OPCRD, so only the CAT score will be used

Moderate / Severe COPD Exacerbation
Where a COPD exacerbation rate will be defined as occurrence of:
1. COPD-related*: unscheduled hospital admission / A&E attendance; OR
2. An acute course** of oral steroids for COPD; OR
3. Antibiotics prescribed with lower respiratory consultation.

Moderate/Severe Exacerbations – sensitivity definition
Where an exacerbation is defined as an occurrence of:
4. COPD-related*: Unscheduled hospital admission / A&E attendance; OR
5. An acute** course of oral steroids with lower respiratory consultation; OR
6. Antibiotics prescribed with lower respiratory consultation.

*COPD-related Hospitalisations: consist of either a definite COPD Emergency Attendance or a definite COPD Hospital Admission; OR a generic hospitalisation read code that has been recorded on the same day as a **Lower Respiratory Consultation** (see below; (a) – (c) only and excluding where the only lower respiratory code recorded on that day was for a lung function test).

**Acute oral steroid use will be defined as all courses:
• That are definitely not maintenance therapy, and/or
• Where dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30mg as directed), and/or
• With no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions.

Where:
• "maintenance therapy" is defined as: daily dosing instructions of ≤10mg Prednisolone or prescriptions for 1mg or 2.5mg Prednisolone tablets where daily dosing instructions are not available.
• ≥1 oral steroid course / hospitalisation / antibiotics prescription occur within 2 weeks of each other, these events will be considered to be the result of the same exacerbation (and will only be counted once).

***Lower Respiratory Consultations -** consist of the following:

    (a) Lower Respiratory read codes (including Asthma, COPD and LRTI read codes)
    (b) Asthma/COPD review codes excl. any monitoring letter codes;
    (c) Lung function and/or asthma monitoring
    (d) Any additional respiratory examinations, referrals, chest X-rays, or events.

Secondary endpoints

1. Annual rate of COPD exacerbations in patients controlled vs non-controlled at index date.

2. Time to the first exacerbation in patients controlled and non controlled at baseline

3. Demographic and clinical characteristics associated with poor COPD control, specifically:
    (a) Age
    (b) Sex
    (c) Height
    (d) Weight
    (e) Therapy (at index date)
    (f) Airway obstruction
    (g) Smoking history (pack years)

ANALYSIS

For variables measured on the interval or ratio scale, summary statistics produced will be:
- Sample size (n)
- Percentage non missing
- Mean
- Variance/standard deviation
- Range (minimum- maximum)
- Median
- Inter-quantile range (25th and 75th percentile)

For categorical variable the summary statistics will include:
- Sample size (n)
- Range (if applicable)
- Count and percentage by category (distribution)

Statistically significant results will be defined as $p<0.05$ and trends as $0.05 \leq p < 0.10$.

Association between COPD control status and the outcome period will be modeled using appropriate statistical methods. The statistical approach to be outlined in the statistical analysis plan (SAP) and will be approved by the lead investigator before the study commences.

To evaluate the interaction of different patient (clincial and demographic) characteristics on the association between control status and outcomes, results will be stratified by:
- Age
- Sex
- Height
- Weight
- Therapy (at index date)
- Airway obstruction
- Smoking history (pack years)

LIMITATIONS OF STUDY DESIGN / ANALYSIS

As with all database studies, a number of limitations exist such as: incomplete data and the need to use proxy measures where explicit data are not available. A further limitation of the OPCRD as a UK primary care database is the limited data available on patients' secondary care contacts (e.g. emergency department attendances, hsoptial admission) and use of other healthcare services (e.g. out of hours, walk-in centres). The limited recording of such data is anticipated to lead to an under-estimate of the true number of exacerbations in the study population.

The data from observational studies should be viewed as one element of the overall evidence base and considered in combination with data from other study designs and is intended as a precursor to a prospective pragmatic trial validation.

DATA DISSEMINATION PLANS

REG is committed to registering all research that it conducts and to publishing all study findings in order to ensure: (i) transparency of its activities and (ii) so that REG-funded research can be used to inform the research and lay community.

At least one abstract from the study will be submitted to a key international respiratory congress (e.g. the European Respiratory Society, American Thoracic Society or similar) and at least one manuscript will be developed and submitted for to a peer review respiratory journal to disseminate the primary elements of the planned analysis.

ETHICS

The OPCRD has been approved by Trent Multi Centre Research Ethics Committee for clinical research use, and this study protocol will be submitted to OPCRD's Anonymised Data Ethics Protocols and Transparency (ADEPT) Committee for approval to sanction the use of the OPCRD for the purposes of the proposed study.

STUDY TEAM

Lead investigator: Marc Miravitlles, Pneumology Department, Vall d' Hebron University Hospital, Barcelona, Spain

David Price: Professor of Primary Care Respiratory Medicine, University of Aberdeen, Aberdeen, UK; Owner of Optimum Patient Care Ltd and Chairman of the Respiratory Effectiveness Group

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Nicolas Roche: University of Paris Descartes, Paris, France

Richard Costello: Royal College of Surgeons, Dublin, Irealnd

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Akio Niimi: Department of Respiratory Medicine, Kyoto University Graduate School of Medicine

Alison Chisholm: Chief Scientific Officer of the Respiratory Effectiveness Group, Cambridge, UK

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8. Cote CG, Pinto-Plata VM, Marin JM, Nekach H, Dordelly LJ, Celli BR. The modified BODE index: validation with mortality in COPD. Eur Respir J. 2008;32:1269-74.

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APPENDIX

Appendix 1: OPCRD COPD Questionnaire

COPD Questionnaire

If you would like **immediate** feedback on your answers to this questionnaire, you can complete it online at www.copdtrak.org

PLEASE ANSWER ALL QUESTIONS ON BOTH SIDES

These questions measure the impact COPD is having on your wellbeing and daily life. For each item place a mark(X) in the box that best describes you currently. Please select only one answer for each question.

	1	2	3	4	5	6	
I never cough	☐	☐	☐	☐	☐	☐	I cough all the time
I have no phlegm (mucus) on my chest at all	☐	☐	☐	☐	☐	☐	My chest is completely full of phlegm (mucus)
My chest does not feel tight at all	☐	☐	☐	☐	☐	☐	My chest feels very tight
When I walk up a hill or one flight of stairs I am not breathless	☐	☐	☐	☐	☐	☐	When I walk up a hill or one flight of stairs I am very breathless
I am not limited doing any activities at home	☐	☐	☐	☐	☐	☐	I am very limited doing activities at home
I am confident leaving my home despite my lung condition	☐	☐	☐	☐	☐	☐	I am not at all confident leaving my home because of my lung condition
I sleep soundly	☐	☐	☐	☐	☐	☐	I don't sleep soundly because of my lung condition
I have lots of energy	☐	☐	☐	☐	☐	☐	I have no energy at all

These questions ask your views about your regular COPD treatment. Please show how much you agree or disagree by marking one box for each statement. Please select only one answer for each question.

	Strongly Disagree	Disagree	Not Sure	Agree	Strongly Agree
I need to take my inhaler(s) regularly	☐	☐	☐	☐	☐
I find my inhaler(s) difficult to use	☐	☐	☐	☐	☐
I worry about the side effects of my COPD inhaler(s)	☐	☐	☐	☐	☐
I have enough information about my inhaler(s)	☐	☐	☐	☐	☐
I would prefer to take my regular COPD medications in a once-a-day dose	☐	☐	☐	☐	☐

Thinking about how often you take your regular COPD treatment during the day: please tick one box

☐ I always take it exactly at the times prescribed   ☐ I occasionally miss the odd dose   ☐ I often miss or forget to take doses   ☐ I take it all once a day- it's easier   ☐ I never take it

Which statement best describes how you take your regular COPD treatment. Please select only one answer.

☐ I take it every day   ☐ I take it some days but others I do not   ☐ I used to take it, but now I do not   ☐ I take it only when I have symptoms   ☐ I never take it

Have you seen a specialist respiratory doctor or nurse outside the practice?   ☐ In the last year   ☐ More than a year ago   ☐ Never

COPD Questionnaire

COPDQ/V10.4 11052011

Thinking about breathlessness, which statement best describes you? Please select only one answer.

- ☐ 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 the level because of breathlessness, or have to stop for breath when walking at your own pace
- ☐ Stopping for breath after about 100m or after a few minutes on the level
- ☐ Too breathless to leave the house, or breathless when dressing/undressing

How many nights in the last week did you wake up because of your COPD symptoms?

☐ 0   ☐ 1   ☐ 2   ☐ 3   ☐ 4   ☐ 5   ☐ 6   ☐ 7

Overall, how severe would you describe your COPD symptoms at night over the last week?

☐ I did not experience any symptoms   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Very severe

These questions are about smoking. Please select only one answer for each question.

| Which best describes you? | ☐ Never smoked | ☐ Used to smoke, but don't now | ☐ Still smoking |

If you smoke, or used to smoke: How many cigarettes do/did you smoke per day?

☐ 1-5   ☐ 6-10   ☐ 11-15   ☐ 16-20   ☐ 21-30   ☐ 31-40   ☐ 41-50   ☐ 50+

How many years have you smoked/did you smoke?

☐ 1-5   ☐ 6-10   ☐ 11-15   ☐ 16-20   ☐ 21-30   ☐ 31-40   ☐ 41-50   ☐ 50+

These questions are about what has happened to you during the past year.

In the past year, have you had the way you use your inhalers(s) checked?   ☐ Yes   ☐ No

In the past year, how many times have you been admitted to hospital with breathing problems?   ☐ 0   ☐ 1   ☐ 2   ☐ 3   ☐ 4   ☐ 5 or more

In the past year, how many times have you had a worsening of your chest symptoms requiring a course of steroid tablets and/or antibiotics?   ☐ 0   ☐ 1   ☐ 2   ☐ 3   ☐ 4   ☐ 5 or more

About your nose: Many people with COPD have trouble with their nose which may interfere with their COPD

Do you have **any** of these symptoms: itchy, runny, blocked nose or sneezing **when you don't have a cold?**

☐ No   ☐ Occasionally and little bother   ☐ Occasionally and quite a bother   ☐ Most days but little bother   ☐ Most days and quite a bother

Thinking about exercise, how much time do you spend doing exercise/activity (eg walking) each day?

☐ None   ☐ 15mins   ☐ 30mins   ☐ 45mins   ☐ 1 hr   ☐ 2 hrs   ☐ 3 hrs or more

In the future, would you be willing to participate in further questionnaire based research?   ☐ Yes   ☐ No

Do you have home oxygen therapy (either cylinders, liquid oxygen or a concentrator)?   ☐ Yes   ☐ No

Thank you for completing this questionnaire. Please return to us in the freepost envelope provided.

Date: 30 June 2015; **Version:** 3

Appendix 2: OPCRD data dictionary

1. Patient

The **Patient** file contains basic patient demographics, patient registration and practice registration details.

Field Name	Content
Patient_ID	Anonymised patient identifier
Practice_ID	Unique practice identifier.
Year_Of_Birth	Patient year of birth in format YYYY
Gender	Patient gender
Status	Patient registration status - (R) – Registered, (L) – Left, (D) - Death
Joined_Date	Date joined practice or date first registered on database
Leaving_Date	Date left practice or date first registered on database
Leaving_Reason	Reason for leaving practice
Post_Code	"Out" part of patient postcode and first character of "in" part of patient post code

2. Clinical

The **Clinical** file contains medical history events. This file contains all the medical history data entered on the GP system, including symptoms, signs and diagnoses. This can be used to identify any clinical diagnoses, and deaths. Patients may have more than one row of data. The data is coded using Read codes, which allows linkage of codes to the medical terms provided.

Field Name	Content
Patient_ID	Anonymised patient identifier
Event_Date	Date of event
Read_Code	Five byte read code for event including terminal code if available
Read_Term	Rubric associated with read_code
Numeric_1	First numeric value if stored
Numeric_2	Second numeric value if stored
Text	First 50 characters of any text associated with entry

3. Referral

The **Referral** file provides details of all referrals for the defined patient cohort identified by a medical code indicating the reason for referral. This table contains information involving patient referrals to external care centres (normally to secondary care locations such as hospitals for inpatient or outpatient care).

Field Name	Content
Patient_ID	Anonymised patient identifier
Event_Date	Date of event in format dd/mm/yyyy
Read_Code	Five byte read code for event including terminal code if available
Read_Term	Rubric associated with read_code
Referral_Type	Referral type e.g. Outpatient
Referral_To	Organisation referred to
Specialism	Referral by e.g. GP referral
Attendance_Type	Attendance type e.g. First visit, follow up

4. Therapy

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The **Therapy** file contains details of all prescriptions on the GP system. This file contains data relating to all prescriptions (for drugs and appliances) issued by the GP. Patients may have more than one row of data. Drug products and appliances are recorded by the GP using the Multilex product code system.

Field Name	Content
Patient_ID	Anonymised patient identifier
Event_Date	Date of event in format dd/mm/yyyy
Drug_Code	Coding for drug
Drug_Term	Drug term associated with drug code
Form	Formulation e.g. inhaler, tablets etc
Dosage	Usage instructions
Quantity	The quantity supplied
numberpack	Number of packs prescribed
packsize	The units of quantity supplied. (the preparation)
issue_ty	Type of issue where A = Acute Issue, R = Repeat Issue
strength	Drug strength
numberdays	Treatment days
bnf_code	BNF code

5. Practice

The **Practice** file contains details for practices, including region and collection information.

Field Name	Content
PracticeID	Unique OPC practice id
Practice_NHS	Unique NHS practice identifier.
Practice_Name	Name of practice
Practice_Address1	Address line 1
Practice_Address2	Address line 2
Practice_Address3	Address line 3
Practice_Address4	Address line 4
Practice_Postcode	Post Code
Practice_list_size	Total practice list size
Last_Extract_Date	Date when practice last did an extract

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Appendix 3: BODE Index

Variables and Point Values Used for the Computation of the Body- Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity (BODE) Index.*[1]

Variable	Points on BODE Index			
	0	1	2	3
FEV1 (% predicted)†	≥65	50-64	36-49	≤35
6-Minute Walk Test (meters)	≥350	250-349	150-249	≤149
MMRC Dyspnea Scale‡	0-1	2	3	4
Body Mass Index§	>21	≤21		

* The cutoff values for the assignment of points are shown for each variable. The total possible values range from 0 to 10. FEV1 denotes forced expiratory volume in one second.

† The FEV1 categories are based on stages identified by the American Thoracic Society.

‡ Scores on the modified Medical Research Council (MMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.

§ The values for body-mass index were 0 or 1 because of the inflection point in the inverse relation between survival and body-mass index at a value of 21.

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