# Patient Centered Outcomes

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**VP & Head, PCO Center of Excellence**

European Federation of Statisticians in the Pharmaceutical Industry
16th Annual Statistical Leaders Meeting

Kastrup, Denmark

May 13, 2025

NOVARTIS | Reimagining Medicine

# Agenda

1. Why Does PCO Matter?
2. How Does it Add Value?
3. How Might this be Structured?
4. Where can Statistical Leaders Contribute?

# Historical aphorisms regarding clinical observation

## "Big Four" including William Osler

***Listen to your patient, he is telling you the diagnosis***

## Johns Hopkins Hospital

***The whole art of medicine is in observation***

***Medicine is a science of uncertainty and an art of probability***

# In regulatory science, methods of observation must meet evidentiary standards

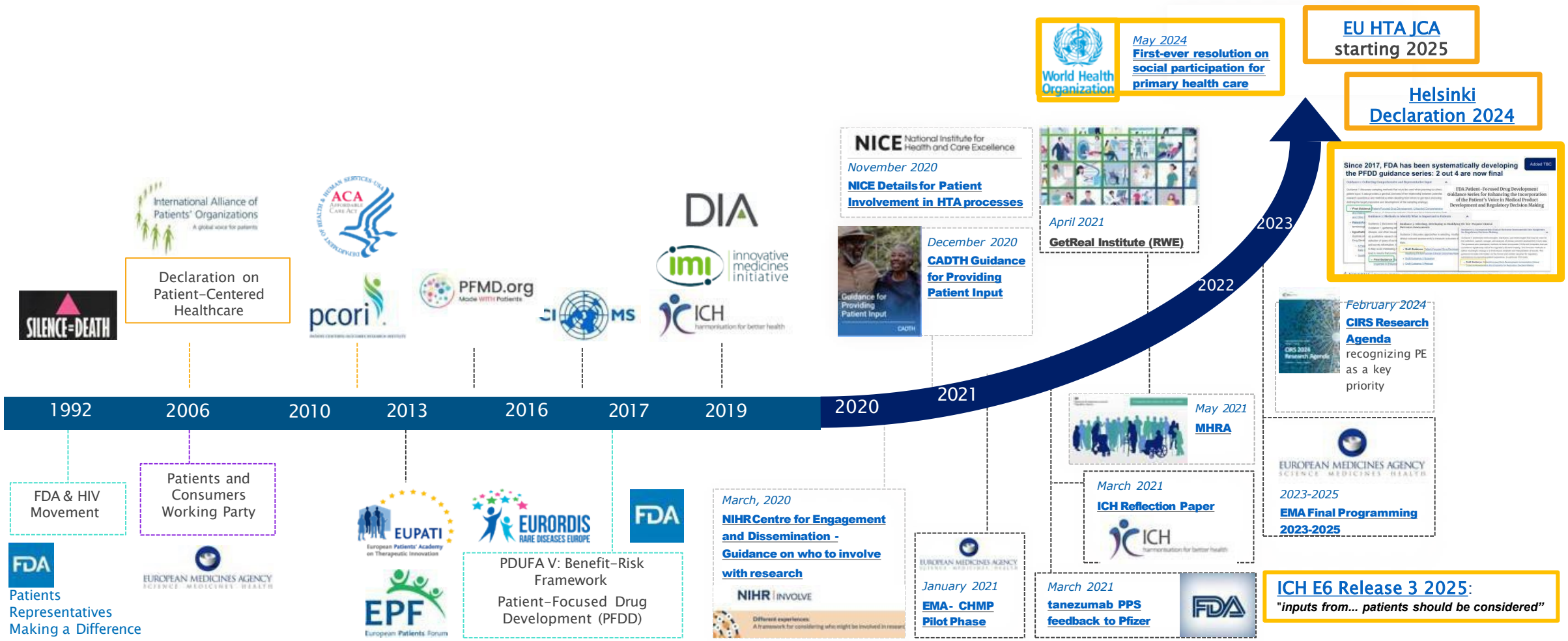

(5) Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data. The protocol and report of the study should describe the procedures used to accomplish this, such as blinding.

(6) The methods of assessment of subjects' response are well-defined and reliable. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and criteria used to assess response.

**Clinical (and other) outcomes have always been key characteristics of adequate and well controlled studies which are critical for regulatory decisions and evidence-based medicine**

**Emerging guidance provides more detailed selection, validation, and analytic frameworks**

# Acceleration of stakeholder demand for robust Patient Experience Data




***Courtesy of and Adopted from:*** *National Health Council, Washington USA, 2023*

# Why does PCO matter?

- Clinical Perspective
- Patient Focused Drug Development:  Guidance and Concepts
- HTA Track Record and Guidance
- Real World Evidence

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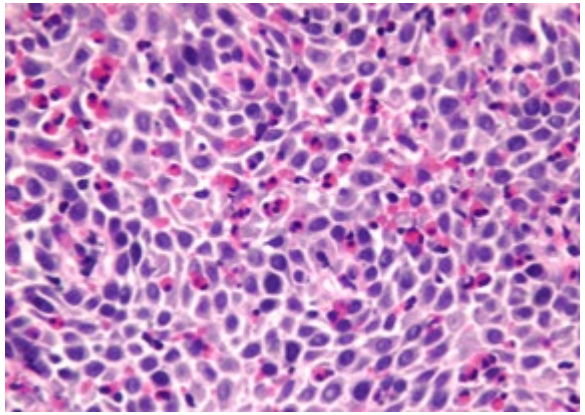
# Eosinophilic Esophagitis (EoE)

**A chronic immune/antigen mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation**

Liacouras C et al., Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011;128(1):3

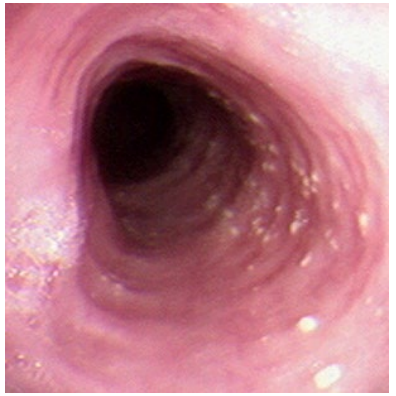


Esophageal biopsy with >40 eosinophils per high power field (HPF) – Maria Botero and Donald Antonioli, Up to Date

**Clinical manifestations include dysphagia and food impaction in adults, dysphagia and abdominal pain in adolescents, and emesis and feeding dysfunction in younger children and infants, respectively**

**Multiple morphological abnormalities may be noted on endoscopy including rings and strictures**

**Treatment options have included dietary therapy, Proton Pump Inhibitors, Glucocorticoids, and Esophageal Dilation**



Multiple rings in the esophagus with papules representing eosinophilic abscesses – Eric Libby, Up to Date

# Need for co-primary endpoints in EoE

## Clinical features and histologic activity can vary independently – treatment goals include resolution or reduction of signs and symptoms as well as histologic remission

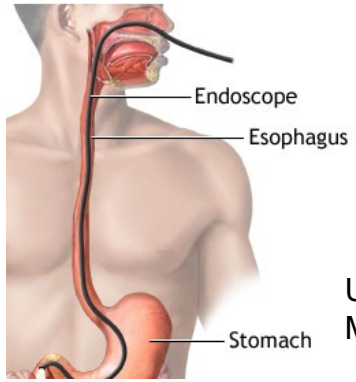
Eosinophilic esophagitis: Developing Drugs for Treatment, Guidance for Industry, US DHHS, FDA, September 2020

**Histologic assessment**

**Esophagogastroduodenoscopy to assess eligibility criteria, 2-4 biopsies in the proximal and distal esophagus respectively as well as follow-up EGD at the final treatment period evaluation**

**Peak Eosinophil count ≤ 6/HPF**

**Difference in proportion of responders across treatment arms**




US DHHS, NIH, NLM, Medline Plus

**Clinical Outcome Assessment**

**Signs/Symptoms which are clinically meaningful based on patient input**

**Group mean differences across treatment arms and assessment of appropriate range of within-patient score change on empirical cumulative distribution function curves**

# FDA Approves First Treatment for Eosinophilic Esophagitis, a Chronic Immune Disorder

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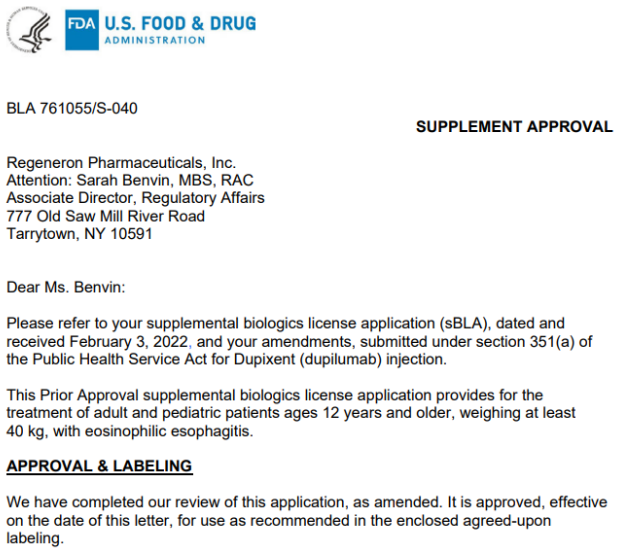
**For Immediate Release:** May 20, 2022

Today, the U.S. Food and Drug Administration approved Dupixent (dupilumab) to treat eosinophilic esophagitis (EoE) in adults and pediatric patients 12 years and older weighing at least 40 kilograms (which is about 88 pounds). Today's action marks the first FDA approval of a treatment for EoE.



FDA U.S. FOOD & DRUG ADMINISTRATION

BLA 761055/S-040

**SUPPLEMENT APPROVAL**

Regeneron Pharmaceuticals, Inc.
Attention: Sarah Benvin, MBS, RAC
Associate Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Ms. Benvin:

Please refer to your supplemental biologics license application (sBLA), dated and received February 3, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Dupixent (dupilumab) injection.

This Prior Approval supplemental biologics license application provides for the treatment of adult and pediatric patients ages 12 years and older, weighing at least 40 kg, with eosinophilic esophagitis.

**APPROVAL & LABELING**

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

"The two primary measurements of efficacy were the proportion of patients who achieved a certain level of reduced eosinophils in the esophagus at week 24, as determined by assessing patients' esophageal tissue under a microscope, and the change in the patient-reported Dysphagia Symptom Questionnaire (DSQ) score from baseline to week 24. The DSQ is a questionnaire designed to measure difficulty swallowing associated with EoE..."

"Assessments incorporating the perspectives from patients with EoE supported that the DSQ score improvement in patients who received Dupixent in the clinical trial was representative of clinically meaningful improvement in dysphagia"

[This approval] "would not have been possible without the implementation of key elements of patient focused drug development…"

Associate Director for Therapeutic Review, Division of Gastroenterology, Office of Immunology and Inflammation, June 30, 2022 FDA public meeting

# Potential roles of Patient Report, Provider Assessment, and Digital Health Technologies in Atopic Dermatitis

## Clinician Reported Outcome

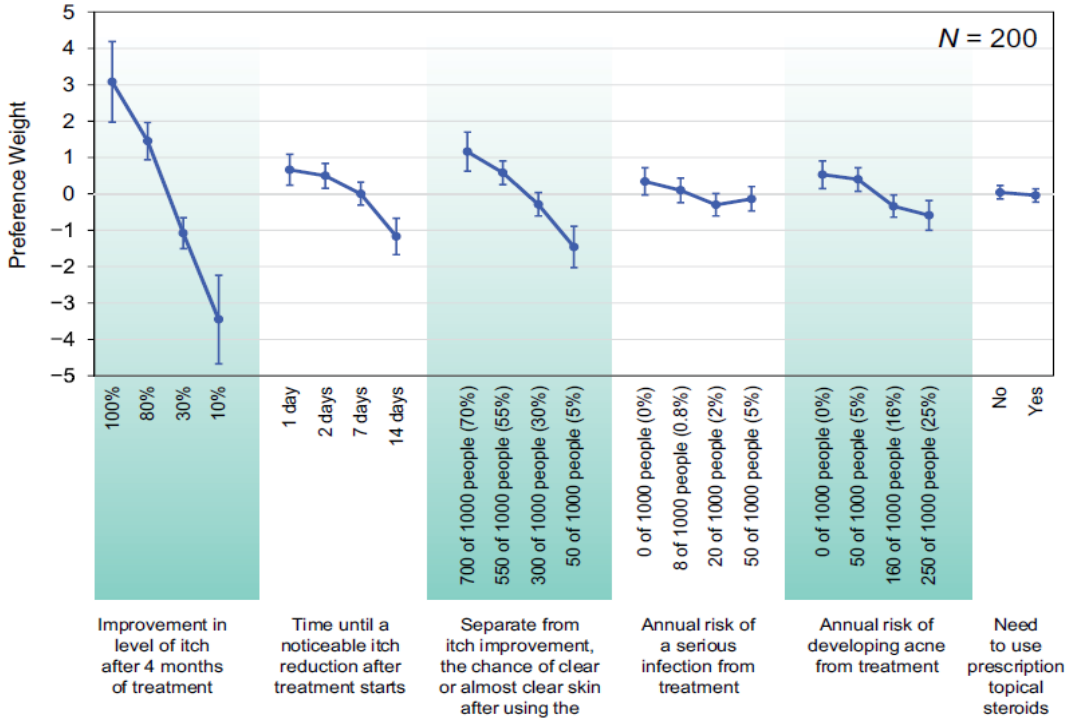
Regulatory trials traditionally rely on the physician-administered Eczema Area and Severity Index (EASI), which captures the extent and severity of skin signs of erythema and edema

## Potential Patient Reported Outcomes

addressing itch, pain, quality of life and sleep quality

**Potential Digital Endpoints** including high-frequency data on scratch and sleep to investigate the speed of onset of effects

**Patient preference study shows patients value improvement in itch & chance of clear skin**



# Incorporating the Patient Voice in Drug Development and Regulatory Decision-Making

| US FDA | European Commission and the EMA | ICH |
|---|---|---|
| Patient Focused Drug Development initiative established in 2012 as part of the fifth authorization of the Prescription Drug User Fee Act (PDUFA V)<br>• Input collected via FDA-led and externally led PFDD meetings<br><br>After passage of the 21st Century Cures Act in 2016 and PDUFA VI in 2017, the Patient Experience Data table was implemented into the review process<br>• Patient experience data *address the impact of a disease or a therapeutic intervention* and *patient preferences with respect to treatment*<br>• Includes patient registries, natural history studies, patient interviews or focus groups, patient survey data, clinical outcome assessment data, and elicited patient preference data<br><br>PFDD guidance documents provide methodological considerations for submission and use in regulatory decision making:<br>• Collecting Comprehensive and Representative Input (2020, final)<br>• Methods to Identify What is Important to Patients (2022, final)<br>• Selecting, Developing or Modifying Fit-for Purpose Clinical Outcomes Assessments (2022)<br>• Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making (2023)<br><br>Current PDUFA VII Framework for the Use of Digital Health Technologies in Drug and Biological Product Development | The new Clinical Trial Regulation (Effective Jan 2022) requires that the application dossier for the initial application shall at least include in the protocol [...] "where patients were involved in the design of the clinical trial, a description of their involvement"<br><br>EMA reflection paper with public comment anticipated by Q4 2025 on the use of patient experience data (PED) in medicines development and regulatory decision-making<br><br>New template for assessors to describe how PED are used in CHMP assessments<br><br>The IMI-PREFER framework went through the EMA qualification process and was deemed appropriate for Patient Preference studies.<br><br>Questions and answers: Qualification of digital technology-based methodologies to support approval of medicinal products (europa.eu) provides key points to consider<br><br>European Commission Regulation (EU) 2021/2282 will advance joint clinical assessments of Health Technologies and includes information sharing with the EMA | The ICH-guideline E8(R1) on General Considerations for Clinical Studies "The choice of endpoints should be meaningful for the intended population and may also take into account the views of patients".<br><br>ICH-guideline M4E(R2) encourages inclusion of the patient perspective in Benefit-Risk Assessment and patient experience data to assess the clinical relevance of potential study endpoints<br><br>ICH reflection paper regarding the need for an ICH guidance on patient-focused drug development published in 2021<br><br>Ongoing ICH E22 working group on Patient Preference Studies will outline the scope for the subsequent guideline to be developed |

# Novartis Patient Centered Outcomes = Clinical Outcome Assessments for Regulatory Agencies and HTAs

## COAs are utilized to evaluate the effectiveness of a medical product in clinical trials

**A COA IS A MEASURE THAT DESCRIBES HOW A PATIENT FEELS, FUNCTIONS, OR SURVIVES. THERE ARE FOUR TYPES OF COAS:**

- Patient-reported outcome (PRO) measures
- Observer-reported outcome (ObsRO) measures
- Clinician-reported outcome (ClinRO) measures
- Performance outcome (PerfO) measures

## COAs are categorized by who is reporting or performing the measurement:

- the patient reports their experience
- the observer reports what they are seeing
- the clinician reports their assessment
- the patient performs an activity

includes Digital Health Technologies as Clinical Outcome Assessments as HA guidance develops

# Importance given to PRO data in HTA Decision-Making

## Level of importance given to PRO data in HTA Decision-Making

**2/3** **Of PROs included in recent HTA appraisals were accepted.**
The Use and acceptance of PROs in HTA appraisals varies across diseases and HTA bodies.
⇒ Using validated PRO measures and validated minimally important difference (MCID) thresholds in well-designed clinical studies are important for the PRO data.

In Germany, assessments by the IQWiG and G-BA, PRO data alone can result in added benefit based on patient-relevant end points such as morbidity and HRQoL.

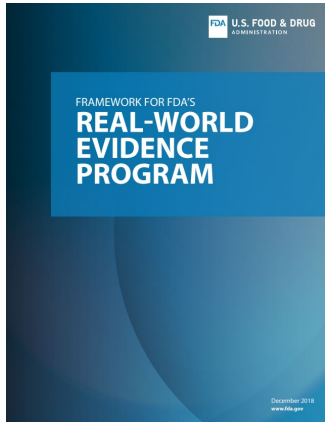
In the UK, NICE's decision-making is driven by cost–effectiveness analysis (CEA) in which the EQ-5D: EuroQol– 5 Dimension (EQ-5D) is a key input to determine health state utilities

HAS Transparency Committee guidance states that besides efficacy and safety data, evidence demonstrating an improvement in HRQoL can lead to a higher clinical added value rating

CDE China's Center for Drug Evaluation issued 1st guidance in 2021 for applying PROs Drug Development. NRDL state patient perspective is important, but impact on NRDL decision-making uncertain

# Real World Data and Clinical Outcomes – United States

## FDA Real World Evidence Framework




- Real World Data are data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources
- **Examples of RWD include...patient-generated data, including from in-home-use settings, and data gathered from other sources than can inform on health status, such as mobile devices**
- Real-World Evidence (RWE) is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD

## Open Source FDA MyStudies App


- **The data storage environment is secure and supports auditing necessary for compliance with 21 CFR Part 11 and the Federal Information Security Management Act, so it can be used for trials under Investigational New Drug oversight.**
- The app is configurable for different therapeutic areas and health outcomes, which reduces software development hurdles for non-FDA users.
- **The data storage environment is partitioned to support multiple clinical trials from different organizations, multi-site trials, or "distributed database" studies**.

# Real World Data and Clinical Outcomes – Europe

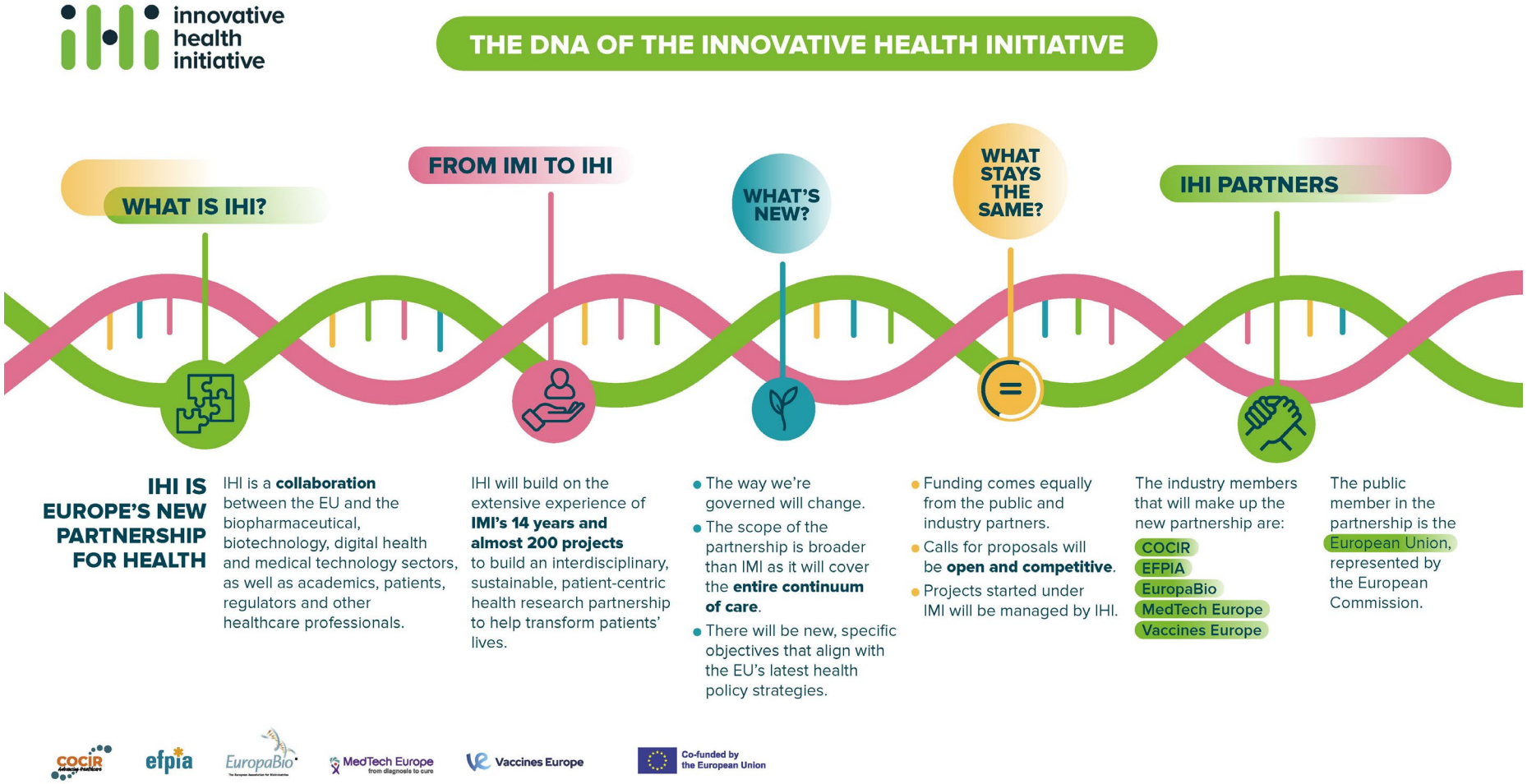
## Objectives

•Pioneer the patient-centred integration of knowledge, technology and products

•Tackle each and every aspect of care to improve lives of patients across Europe and beyond

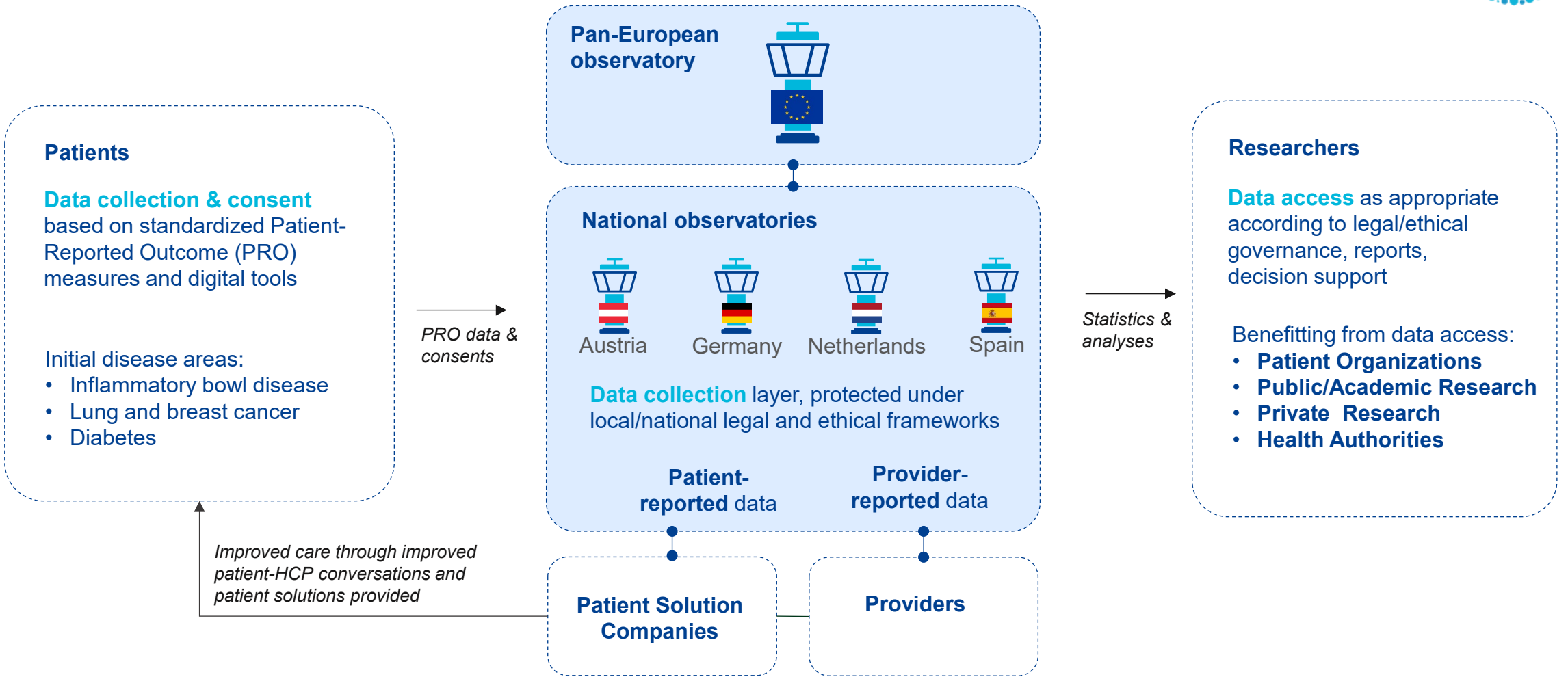
•Strengthen Europe's position at the forefront of medical innovation

•Address current and future health challenges



HOW H2O WORKS

# IMI Health Outcomes Observatory




Courtesy Rahim Lalji

# Key H2O Accomplishments

- **Created Standardized Core outcomes sets** (PROs + Clinical data) that can be captured digitally in routine care for 5 disease areas (Cancer - Breast + Lung + Multiple Myeloma), IBD and diabetes)
- **Established Pan-European Observatory in partnership with regulators**
  - Creates the forum for standardization of patient outcomes that can be measured digitally in routine care
  - Legal entity set up in collaboration with regulators and European Patient Forum
- **Four National Observatories supporting recruitment into the ecosystem in Spain, Austria, Germany, and the Netherlands**
- **Created data governance & access framework**
- **H2O Insights Centre: data visualization platform for aggregated analyses across H2O** (patient descriptive statistics, stratified by factors such as primary indication, comorbidities, drug therapy modalities, demographics, and healthcare institutions)

European Commission Innovation Radar Awards given to H2O for:

- Patient Agreement
- Core outcome sets tested for digital implementability in routine care
- Multistakeholder governance model for health data management

The Innovation Radar is a European Commission initiative to identify high potential innovations and innovators in EU-funded research and innovation projects

## PCO CoE areas of focus for 2025

- **WP1: Governance, Sustainability, Capabilities**
- **WP2: Technical Infrastructure and Interoperability** ("PROMOPing")
- **WP 6: Communication and Analysis** (co-leadership; ms)

Adapted from Rahim Lalji

# How does it add value?

- Authorization
- Access
- Adoption

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# Our patient-centered outcomes mission

## Optimize patient-centered outcome strategies and execution with program teams to enable successful authorization, access and clinical adoption

**Patient Needs**

**Regulators' Requirements**

**HTA agencies' expectations**

**Value creation**

**Patients and HCPs**


**Novartis**

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# Emerging roles in oncology:  Dose Optimization

## Friends of Cancer Research White Paper

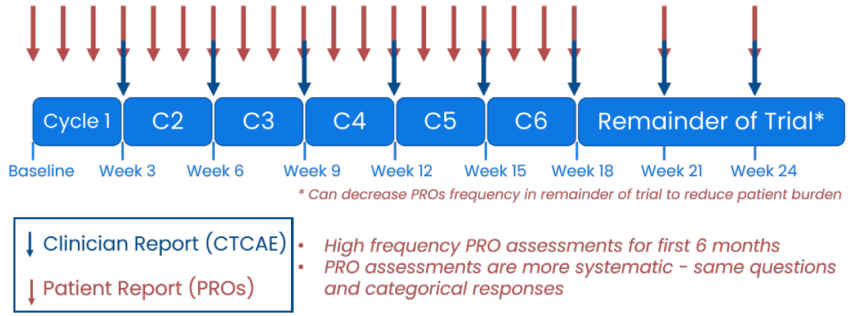
- Even lower grade symptomatic adverse events may become burdensome over long treatment periods
- The patient is in the best position to report “unobservable” symptoms such as nausea
- Innovative therapies with an oral daily dose may appear “less tolerable” relative to chemotherapy if investigator assessments only are used and symptoms have started to resolve

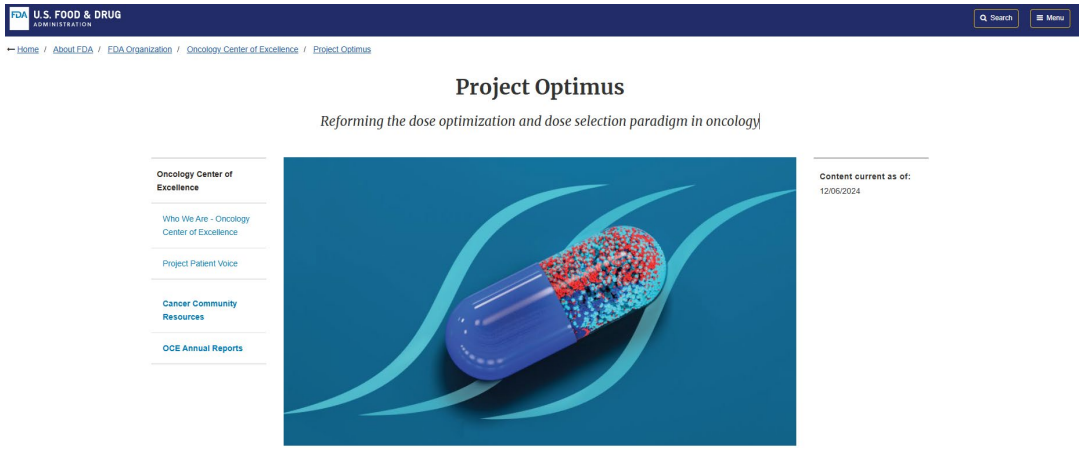
## FDA Project Optimus

Move forward with a dose-finding and dose optimization paradigm across oncology that emphasizes selection of a dose or doses that maximizes not only the efficacy of a drug but the safety and tolerability as well

FRIENDS of CANCER RESEARCH

**Figure 2: Frequency of PRO assessments.** PRO symptom data provides more consistent data capture by asking the same question with categorical response options at a higher frequency. This data source can add power to exposure-response analyses during Dose Escalation study. High frequency PRO assessment can be reduced later in trial by asking a comprehensive PRO assessment at several longer-term cross-sectional time points (e.g., 1 year, 2 year, etc.). *Adapted from figure courtesy of Zirkelbach, Bhatnagar, and Kluetz.*



# Emerging roles in oncology: Supporting overall benefit-risk evaluation, EU SmPC, and HTA


## Takeaways:

PROs can reflect treatment efficacy (reduction in disease-related symptoms) or harms (symptomatic adverse events) as well as impact on functioning.

PRO data are usually reflected in European Public Assessment Reports. Multidimensional HRQOL are advantageous for HTA.

Methodological issues and “clinical relevance” have often prevented inclusion in the SmPC. Development of standards is ongoing

# European vs. US Perspectives regarding Oncology PCO

## Europe

- “Core measure” - functioning, common symptoms and adverse events, and HRQOL
- Disease specific module
- Item list particularly for adverse events not expected to be covered by the core for a novel treatment

## US

- Disease symptoms
- Symptomatic adverse events
- Overall side-effect burden
- Physical Functioning
- Role Functioning

Perspectives

Using patient-reported outcomes and health-related quality of life data in regulatory decisions on cancer treatment: highlights from an EMA-EORTC workshop

Introduction

The benefit-risk assessment of cancer treatments usually focuses on traditional clinical and disease outcomes, such as overall survival, progression-free survival, and tumour response, balanced against clinician-reported adverse events. Patient-reported outcomes (PROs) measuring symptoms, functioning, and other health-related quality of life (HRQOL) impacts can be used to ensure that a drug's effect on symptoms and functioning are quantified and evaluated as part of cancer clinical research and drug development. However, the impact of PROs on regulatory assessment and health technology assessment (HTA) can vary due to issues related to study design, PRO item selection, assessment frequency, study conduct, and handling of data missingness.

To address these issues, the European Medicines Agency (EMA) and the European Organisation for Research and Treatment of Cancer (EORTC) organised a joint workshop in 2024. This Perspective highlights the key discussions during this workshop and provides proposed solutions to generate evidence that benefits shared decision making between clinicians and patients.

Well-defined PRO research objectives

A commonly shared view across various international stakeholders was that PROs intended to provide quantitative assessment of clinical outcomes should be treated like any other endpoint that is included in the evaluation of a cancer treatment. Thus, an important first step is to clearly describe the research questions that PROs can address to support the evaluation of cancer treatments. PROs are not an outcome but a way to measure an outcome; therefore, it is important to identify in the objectives which outcome will be measured. For example, a trial objective of comparing PROs between treatment A and treatment B is not a precise description of an objective or endpoint. Having such objectives will result in multiple ways the PRO data can be analysed, which can lead to potentially disparate reporting and conflicting results. Instead, the research question needs to be well described in the protocol so that an adequate design and analysis method can be selected to ensure that the results truly address the intended research question.[12]

Role of submitted PRO data for decision making

Further optimisation in the use of PROs is necessary to fully leverage the insights patient-generated data can provide.[4,5]

Support overall benefit-risk evaluation

PROs can quantify symptoms and functional aspects of how patients experience and respond to their treatment and can complement traditional clinical endpoints such as overall survival, progression-free survival, and tumour response measures. PRO data can reflect treatment efficacy (ie, improvement in disease-related symptoms) or harms (ie, emergence of symptomatic adverse events and their impact on functioning). By incorporating these additional outcomes into clinical trials, a more holistic understanding of benefits and harms can inform regulatory and clinical decision making. PRO data are usually reflected in publicly available assessment reports, such as the European Public Assessment Reports (EPARs) in Europe.

Further characterise tolerability

One research objective that is relevant across early phase and late phase clinical cancer trials is to characterise safety and tolerability. It has been proposed that a complete understanding of tolerability should include direct measurement from the patient on how they are feeling and functioning when on treatment.[3] For example, patient-reported symptomatic adverse events can complement standard safety reporting by clinicians. Understanding treatment tolerability can help corroborate or refine the understanding of more traditionally collected toxicity data. As such, incorporating PROs to inform tolerability could be a consistent objective across all oncology trials, including early trials evaluating the optimal dose and administration schedule or expansion studies evaluating early efficacy.[7]

Product information and label

A common goal for commercial sponsors is to use PROs to support medicines' approval, labelling, or marketing claims of treatment benefit. However, methodological issues, PRO data quality (including high rates of missing data or asymmetric missing data), and the question of what makes a clinically relevant PRO result have often prevented their inclusion in the product label (eg, EU Summary of Product Characteristics).[3] Development of PRO standards to address these methodological issues is currently ongoing.[8] High-quality PRO data can be conveyed to the public through other channels to further inform tolerability rather than a comparative efficacy claim. For instance, the US Food and Drug Administration (FDA) Oncology Center of Excellence has developed a web-based communication platform, called Project Patient Voice, to display PRO results that inform tolerability from cancer clinical trials.[9]

www.thelancet.com/oncology Published online April 14, 2025 https://doi.org/10.1016/S1470-2045(25)00150-0 1

Lancet Oncol 2025
Published Online April 14, 2025 https://doi.org/10.1016/S1470-2045(25)00150-0
See Online/Comment https://doi.org/10.1016/S1470-2045(25)00151-2



Core Patient-Reported Outcomes in Cancer Clinical Trials
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2024
Clinical/Medical



Lancet Oncol Published **Online** April 14, 2025 https://doi.org/10.1016/S1470-2045(25)00150-0

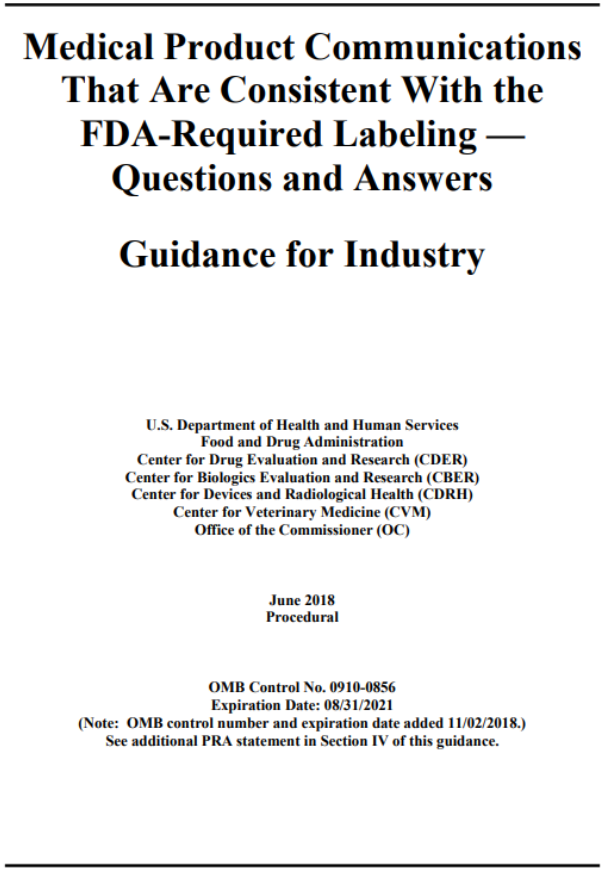
# CFL communication: effects of the product on the Patient

## As described in the CFL guidance:

FDA labeling is not intended to exhaustively address all that is known about a product for its approved or cleared uses

Opportunity exists to provide information concerning the effects of a product on the patient for its FDA approved indication in its approved patient population

Additional data and information may be communicated if it is consistent with the FDA required labeling in a truthful and non-misleading way



**Medical Product Communications That Are Consistent With the FDA-Required Labeling — Questions and Answers**

**Guidance for Industry**

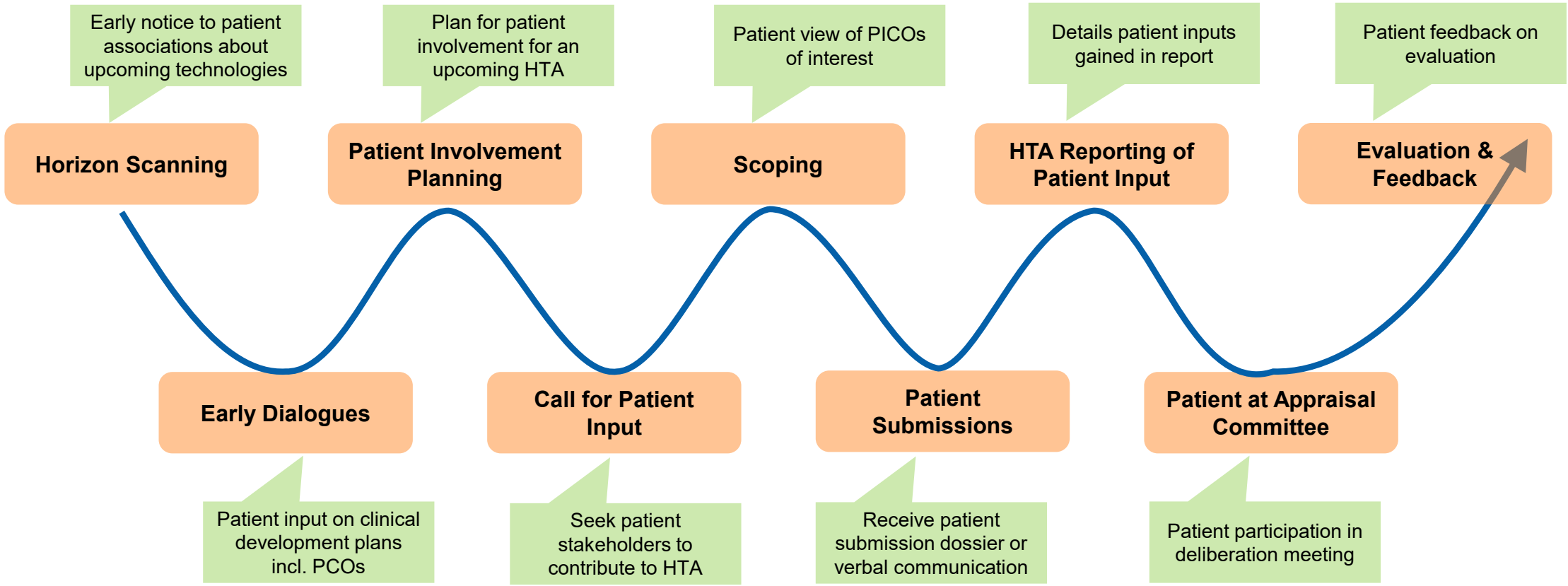
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Veterinary Medicine (CVM)
Office of the Commissioner (OC)

June 2018
Procedural

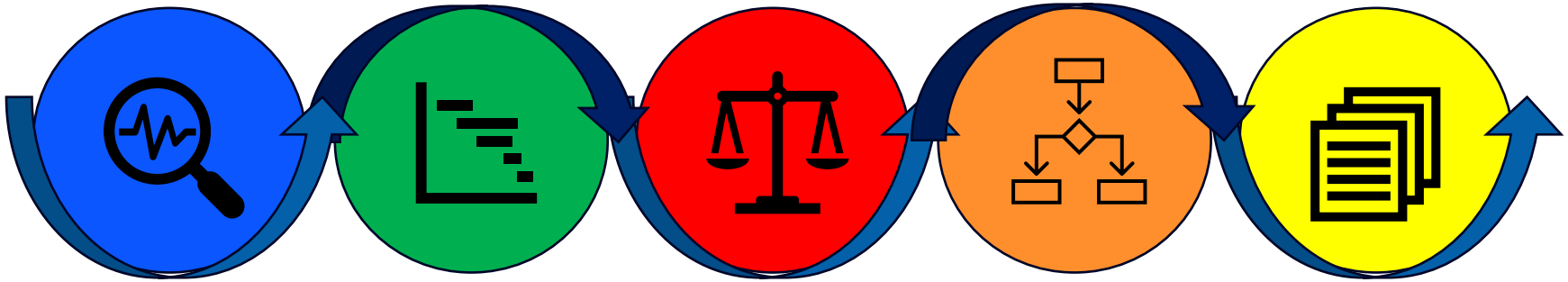
OMB Control No. 0910-0856
Expiration Date: 08/31/2021
(Note: OMB control number and expiration date added 11/02/2018.)
See additional PRA statement in Section IV of this guidance.

# Inclusion of PCOs and/or Patient Voice in HTA evaluations
*via patient insights / patient relevant data / patient influence*

**Important!** Having a clear Patient strategy to what to prioritize for each TA/Brand



# HTA submissions: inclusion of PCOs/PROs




**Incl. Disease Description, Epidemiology, Burden of Disease, Patient Burden...**

**Incl. Meta-Analyses, Indirect Treatment Comparisons incl. PROs**

**Incl. Added Value versus SoC via COAs & PCOs**

**Incl. Utilities to estimate cost-utility ratios** (Cost of tx A – Cost of tx B / Utility Tx A – Utility tx B)

**Incl. Decision Problem, Burden of Disease, Clinical Effectiveness, Cost-Effectiveness Model, BIM**



BIM: Budget Impact Model; SoC: Standard of Care

# How might this be structured?

- Roles
- Prioritization
- Activities

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# Your feedback from the survey

## Selected abridged responses

### How does your company incorporate a patient focus into drug/biologic development?

We use more patient related clinical outcomes in our phase III trials, but personally think we can do more and better.

Dedicated division with remit for patient centric DD.

Not yet established a systematic approach to incorporating the patient's perspectives and preferences into the development. Started a bit within rare disease

### Has one of your development programs been impacted positively or negatively by the clinical outcome and endpoint development process and what did you learn?

too much resource spent on it for a low impact.

...requirements around validation are often perceived as a hindrance..

Example of pivotal study with primary endpoint being PRO and clinical important difference not well understood

Unvalidated digital endpoints used for PoC and failing at regulatory consultation by lack of team ownership to investigate and question the endpoint. One learning: proper endpoint validation may require cross -industry consortia and efforts.

### What are the most significant challenges that you face within your statistical organizations to work with clinical trial teams to develop clinical outcome assessments and endpoints?

The assumption that something is automatically valid (and does not require separate validation).

Change management of perception (soft science) to relevant part of the value determination and positioning of a new therapeutic

established COAs and PROs do not meet needs regarding development objectives and compound specifics

Using distribution and anchor methods is rather new.

lot of discussions , not clear plan of what is mandatory, nice to have, many stakeholders

### Have you considered insourcing some of these activities, and do you believe internal statisticians could or should lead some of these activities? Which skill sets do you have within your organizations and which skill sets do you need?

Basic understanding and skills are present in the organization for having a dialog with vendors but more is needed but we can lead these activities

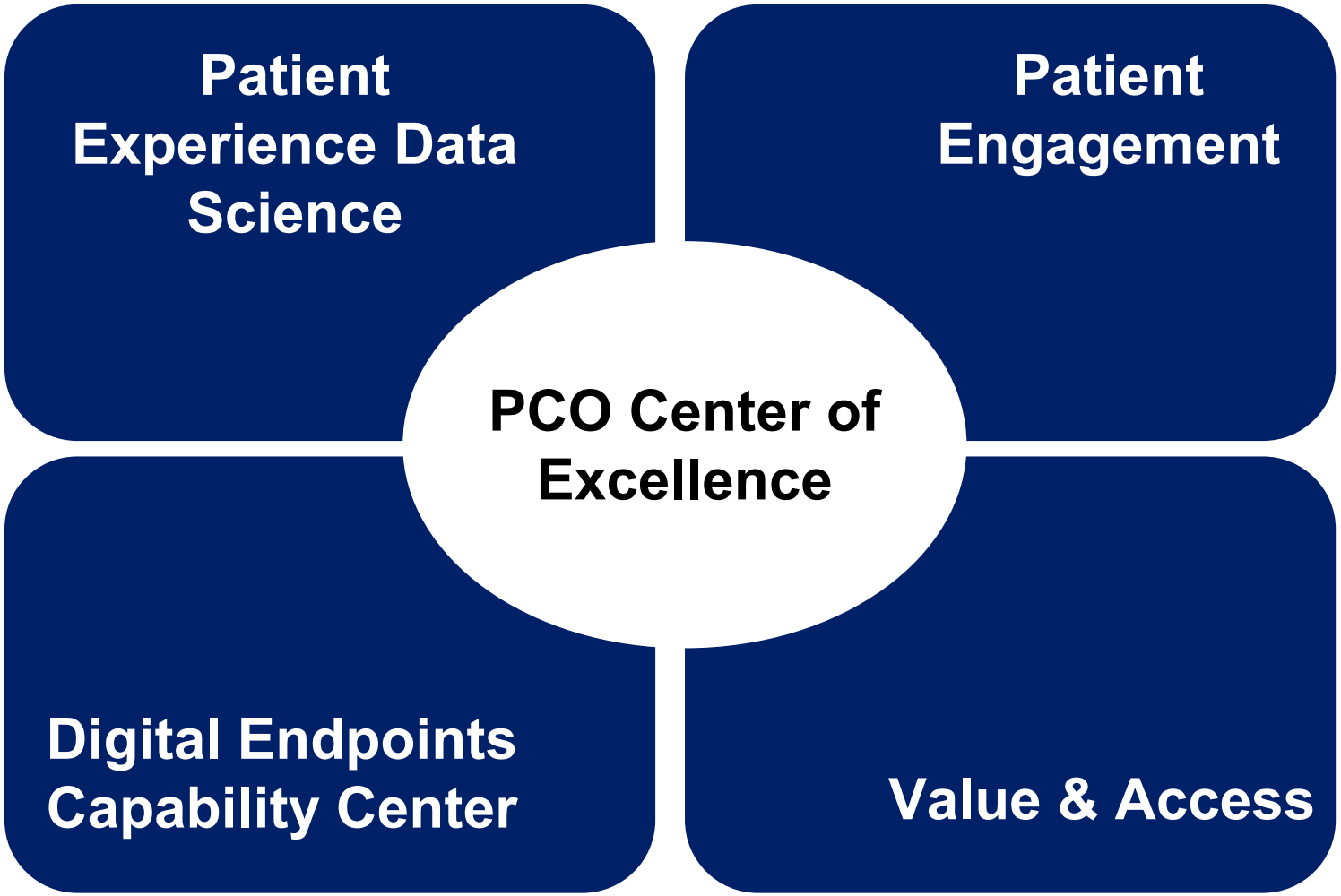
We would see statisticians as collaborators but not the obvious leaders for this work

I believe the internal team should at least be in position of providing an efficient oversight, which means first that the internal team is involved, secondly that they have the aptitude to understand what is important or not for the patient. This is why direct access to the patients could be an very important condition.

Yes, statisticians should play a central role

Endpoint development is critical and expensive. You always learn a lot, but my biggest takeaway is that it is very easy to get scammed by startups.

# OnePCO at Novartis



# Prioritization Points to Consider

- COA endpoint(s) critical for approval: Primary or key secondary endpoint
- Development Priority Status
- First in indication, No COA precedent or No validated COA
- Differentiation Needed
- Other/Team Request

# Clear roles and responsibilities established between BR, PE and PA

*Together we will embed insights across the lifecycle, co-create solutions and collaborations across the patient community*

**BR Patient Insights and Experience (PIE) works across scientific and clinical teams in BR in collaboration with the patient community to ensure we are developing drugs that patients want and creating patient-friendly early trials**

**Patient Engagement (PE) drives systematic collaboration with the patient community and other stakeholders, in support of our Development programs**

**Patient Advocacy (PA) collaborates systematically and consistently with patient communities, gathering insights and driving programs that mobilize patients to seek optimal care, improve health outcomes and accelerate access to innovative medicines**

In drug discovery phase, PIE incorporates **quality patient input** obtained through relevant patient community to ensure that patient priorities are considered and that ultimately the product addresses the outcomes that matter most to patients

Create positive changes for patients by understanding what matters most to patients and make choices that focus on where we can create the greatest impact. PIE lays the groundwork for value proposition and label of future drugs by ensuring endpoints important to patients are part of development from the start.

Work across the full spectrum of research, development and medical affairs

Provide early and continued input (e.g., TPP, CDP, IEP), ensuring decisions across the medicine lifecycle are rooted in patient's experiences, perspectives and priorities to meet regulatory and HTA bodies' expectations

Leads initiatives that mobilize patients to seek the best treatment/care as well as above brand policy and healthcare system shaping to reduce systemic barriers to care

Partners with the commercial organization to bring the external lens to help define and lead Novartis Therapeutic Area disease and medicine patient advocacy and mobilization strategies

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Courtesy Christy Greeley and Michaela Dinboeck

# Disentangling digital biomarkers, electronic COAs & digital endpoints

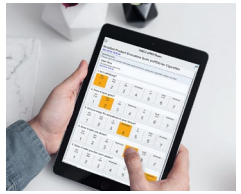
## Digital Endpoints

### Clinical Outcome Assessments (COA)

or

### Biomarkers

Established | Novel



## eCOA

DHTs such as a tablets, smartphones, smart watches, etc. may be used to collect **established endpoints** pertaining to how a patient feels or functions (PRO, PerfO, ClinRO, ObsRO).

- e.g. daily pain NRS completed outside of the clinic.


## DHT COA [FDA 2, EMA4]

DHTs such as a tablets, smartphones, smart watches etc may be used to collect **novel endpoints** pertaining to how a patient feels or functions.

- Moderate to Vigorous Physical Activity (Actigraph): Ph3 primary E/P: Fibrotic Interstitial Lung Disease (Bellerophon)
- Stride Velocity 95 Centile (Sysnav): Primary E/P approved by EMA: Duchenne's Muscular Dystrophy
- Nocturnal Scratch: Potential secondary E/P: Atopic Dermatitis (Abbvie)

## Digital Biomarker [FDA 2,3]

DHTs such as a tablets, smartphones, smart watches etc may be used to collect measure of physiology and/or behaviour as an indicator of biological, pathological process or response to an exposure or an intervention. The clinical meaning is established by a reliable relationship to an existing, validated endpoint.

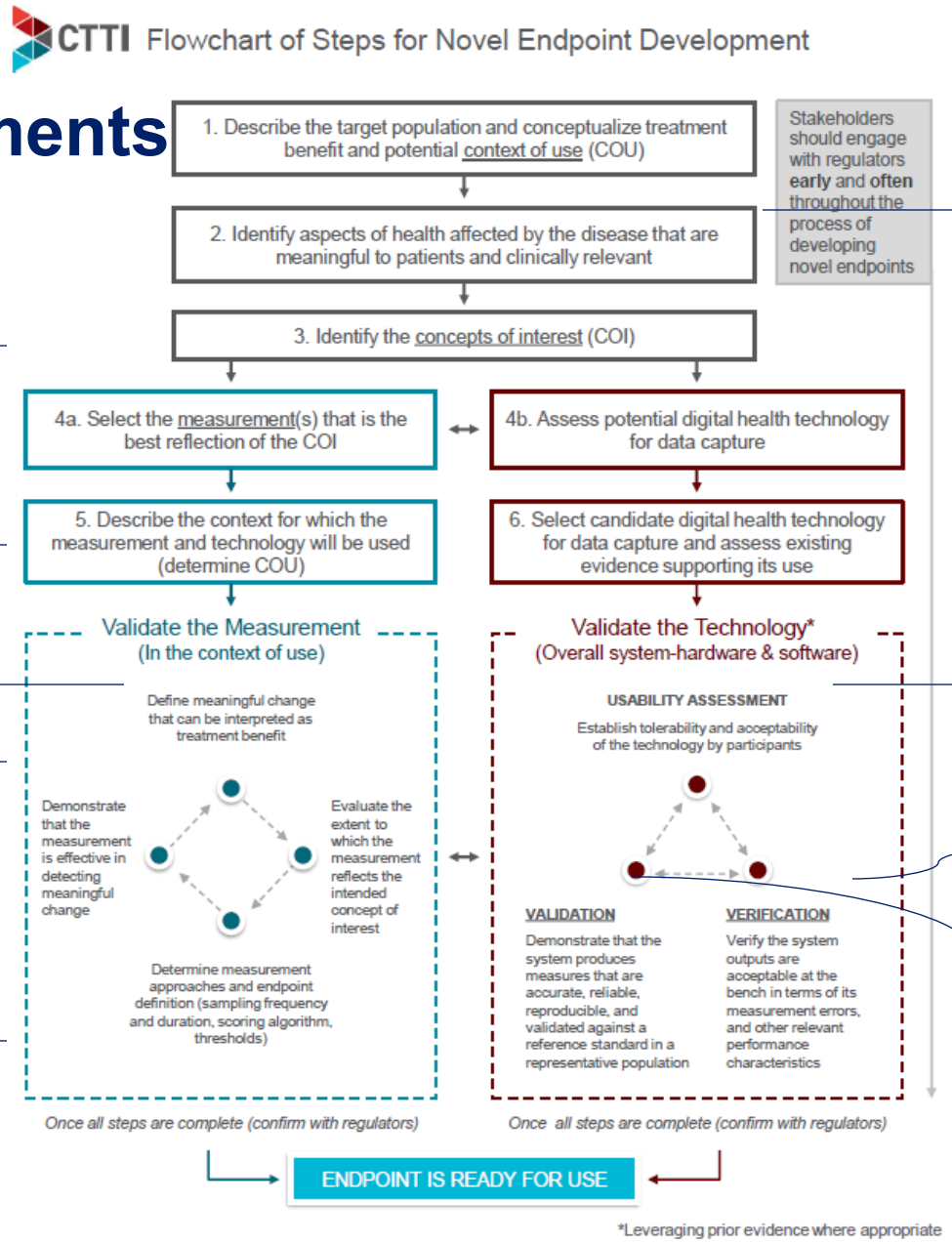
- e.g continuous glucose monitoring (patch sensor) to measure response and/or safety.


1. Why Language Matters in Digital Endpoint Development: Harmonized Terminology as a Key Prerequisite for Evidence Generation | Digital Biomarkers | Karger Publishers
2. Digital Health Technologies for Remote Data Acquisition in Clinical Investigations | FDA
3. BEST (Biomarkers, EndpointS, and other Tools) Resource - NCBI Bookshelf (nih.gov)
4. Questions and answers: Qualification of digital technology-based methodologies to support approval of medicinal products (europa.eu)
5. Patient Focused Drug Development Guidelines | FDA




Courtesy of Lorcan Walsh

# Digital Endpoint evidentiary requirements (COA)




**Clinical Meaningfulness –** do the measures mean anything to the patients & do changes impact their lives.

**Measurement selection** – picking the most appropriate measurements & defining COU.

**Technology selection/ feasibility** – selecting most appropriate DHT for the context of use

**Meaningful Change –** are changes in the measure meaningful to patients and/or what magnitude of change is important.

**Usability/acceptability of the tech –** is the technology easy to use for the patients and/or clinicians.

**Clinical Validation –** identifies, measures, or predicts the clinical, biological, physical, functional state, or experience.

**Technical Verification** – do the sensors measure the raw data as expected.

**Analytical Validation** – does the technology measure what we expect it to measure accurately and reliably.

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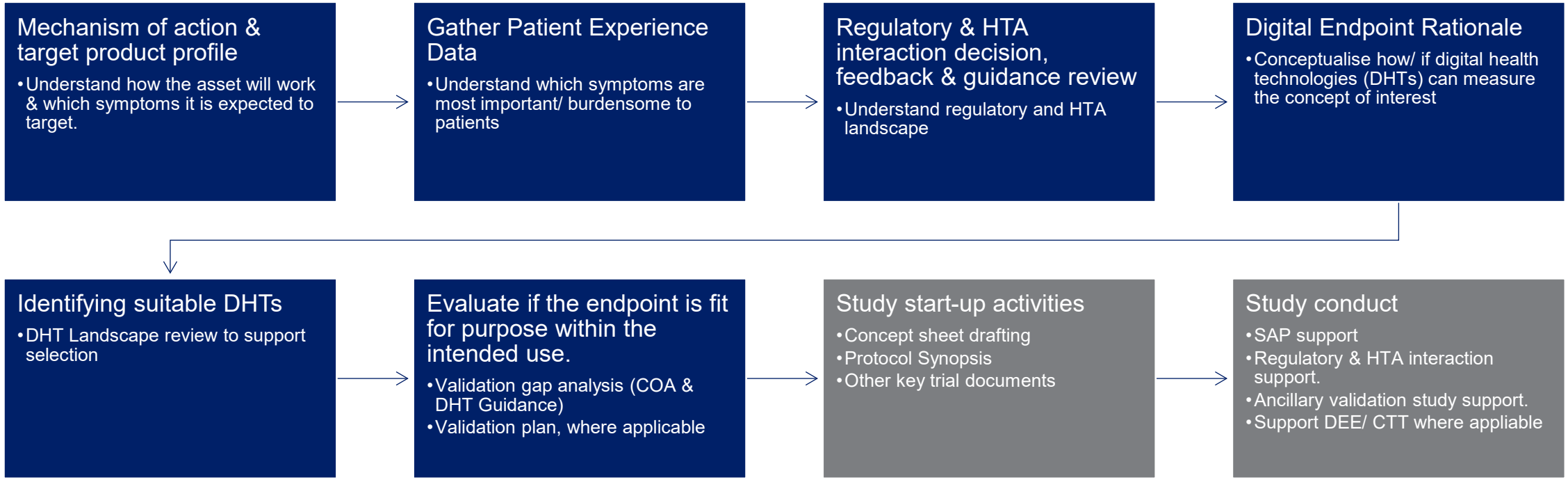
1. Flowchart: Steps For Novel Endpoint Development - CTTI (ctti-clinicaltrials.org)

# Digital Endpoint Strategy Development




This process may vary based on the study phase and purpose of the endpoint.



Courtesy of Lorcan Walsh

# OnePCO strategy


**Deliverables:**
**OnePCO strategy**

Consisting of

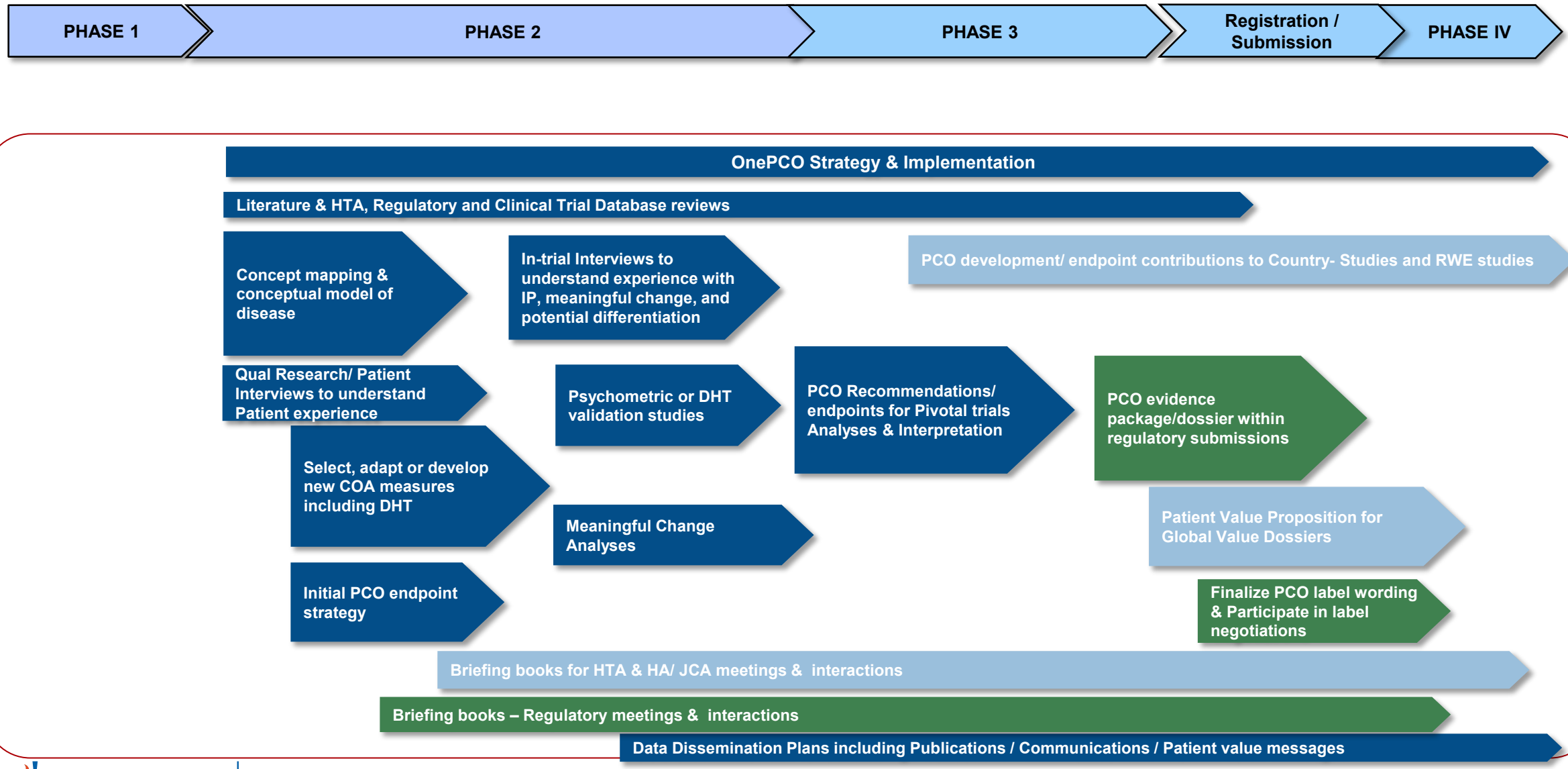
- **Concept of interest**
- **Rationale and Evidence Supporting COAs**
- **Gap analysis**
- **Execution plan**

**Note**: not all aspects will be relevant to every project.



Courtesy of Conny Berlin and Michaela Dinboeck

# PCO aligned against the lifecycle: schematic



# Where can Statistical Leaders Contribute?

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# Design, Methods, Reporting

**Qualitative Studies**
Sampling, AI enabled extraction of Concepts of Interest, Concept Saturation

**Estimand framework and endpoint construction**

**Patient Preference Studies**

**Missing Data**
High volume and frequency

**Instrument (or DHT) design and validation**

**RWE**
Approaches to inclusion of baseline PCO/DHT in confounding control methods for non-interventional studies

**Meaningful Change**

**Optimal Planning and Reporting**
Concepts, SAPs, Protocols, Study Reports, Publications

# Industry Leadership and Regulatory/HTA Decision Frameworks

## PCO is a cross functional activity

- Clinical, quantitative, and operational perspectives differentiate successful PCO within industry
- This is another internal leadership opportunity for experienced statisticians

## Patient centric approaches as well as regulatory and access convergence will help drive continued evolution in guidance and practice

- Industry statisticians are well versed in the broader decision frameworks and can contribute to multistakeholder efforts
  - Helping international regulatory agencies and HTAs describe what they need from PCOs – substantial evidence, supportive evidence, comparative evidence, other contextual information
  - Assisting with harmonization efforts across the lifecycle and across regions/countries

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**Acknowledgements:**
Michaela Dinboeck
Conny Berlin
Christy Greeley
Sue Vallow
Karina Hansen
Lorcan Walsh
Mareile Hark
*and the teams within PE, PED Science, V&A, DECC, and the CoE*

# Thank you

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