Patient Focussed Digital Health Technology

PSI PFDD SIG Meeting

June 2024

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Patient Focussed Digital Health Technology

- Digital biomarkers and clinical outcomes assessments
- Are Electronic COAs just another PerfO?
- How can I use an Electronic COA in a trial?
- Can I just “chuck in” a digital measurement product?
- How can I analyze the data?

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Digital health technologies can be used in different ways

As a Biomarker

"*A defined characteristic that is measured as. an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions*"

They are a data stream or a collection of data streams used to make an assessment about something, but are not necessarily related to the patient experience

As a Clinical Outcomes Assessment

"*A clinical outcome assessment (COA) describes or reflects how a person feels, functions, or survives and can be reported by a healthcare provider, a patient, a non-clinical observer (such as a parent), or through performance of an activity or task*"

COAs are patient relevant data - either reported from the patient or recorded from the patient about something that matters to them

Source: BEST guidelines, COAs in Medical Device Development

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There are 7 types of biomarkers

Diagnostic Biomarker

Monitoring Biomarker

Pharmacodynamic / Response Biomarker

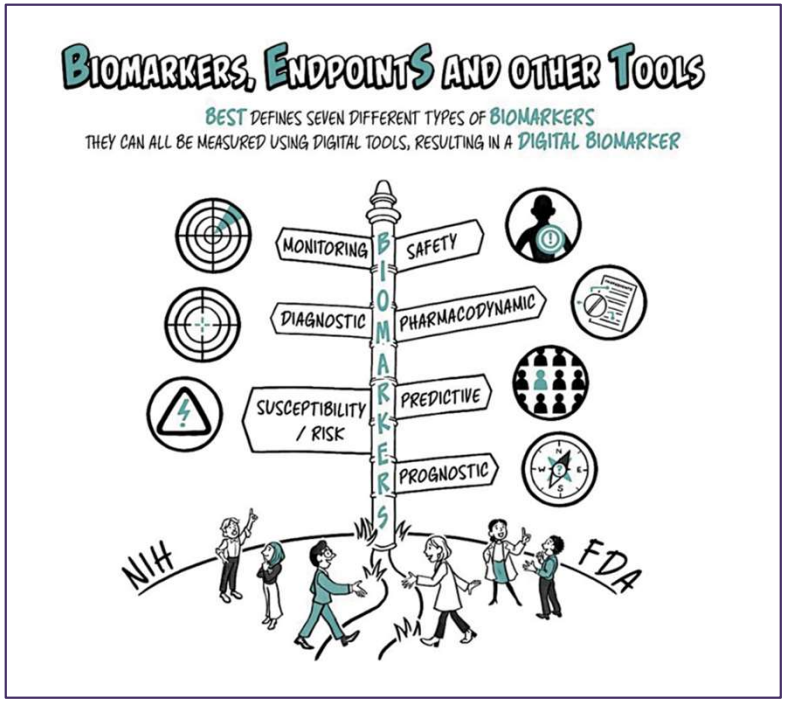
Predictive Biomarker

Safety Biomarker

Susceptibility / Risk Biomarker

Prognostic Biomarker

When a biomarker is collected using a digital sensing product, it is a ***digital biomarker***.



Source: FDA Facts: Biomarkers and Surrogate Endpoints Karger - Digital Medicine: A Primer on Measurement *The Playbook*

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Clinical outcomes assessments are related to the patient and their experience

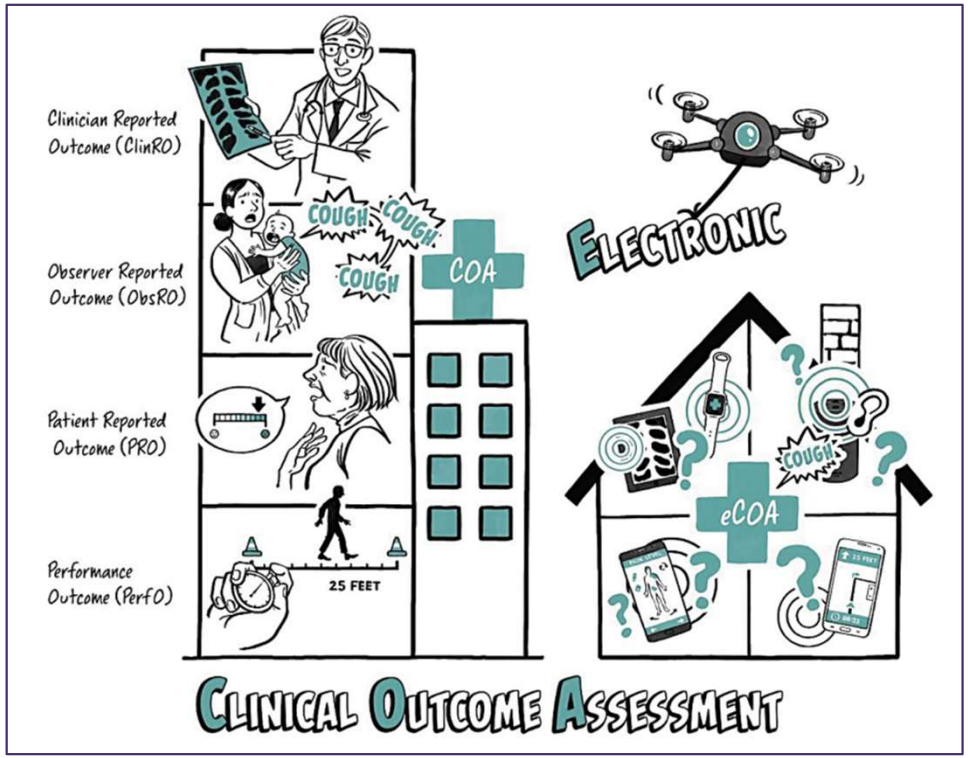
Clinician reported outcome (**ClinRO**)

Observer reported outcome (**ObsRO**)

Patient reported outcome (**PRO**)

Performance outcome (**PerfO**)

When a **COA** is collected using a digital technology, it is called an ***electronic outcome assessment*** or ***'eCOA'***. Note not all eCOAs are collected using a sensor. Ex: ePROs



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Aren't DHT's just another PerfO?

Performance Outcomes (PerfOs)

Initial Definition

*"A measurement **based on a task(s)** performed by a patient according to instructions that is **administered by a health care professional**."*[1]

Updated Definition

*"A measurement **based on a standardized task** performed by a patient that is **administered and evaluated by an appropriately trained individual** or is **independently completed**."*[2]

Digital Health Technology as eCOAs

"Digital health technologies use computing platforms, connectivity, software, and sensors for **health care and related uses**.

"They include technologies intended for use as a medical product, in a medical product, as companion diagnostics, or as an adjunct to other medical products (devices, drugs, and biologics). **They may also be used to develop or study medical products**."

Example: Measuring Gait

Timed 25 foot walk test in clinic
- using a stopwatch
- Interpreted by a clinician

Timed 25 foot walk test at home
- using a smartphone app
- Interpreted by a clinician

Measured walking behaviour in day-to-day life
- using a wearable
- Interpreted in terms of impact to patient

Source: FDA Facts: Biomarkers and Surrogate Endpoints, Richardson et al;, Manor et al.,

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How can I use an Electronic COA in a trial?

Label Based Endpoint Claims

Early Phase Internal Exploration

This is where a lot of the hype rests…

eCOAs are a tool that could be appropriate for use in an alpha controlled endpoint hierarchy

However, this should be dictated by the study needs

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Bellerophon THERAPEUTICS

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Bellerophon Announces FDA Acceptance of Change to Ongoing Phase 3 REBUILD Study of INOpulse® for Treatment of Fibrotic Interstitial Lung Disease

The new study size of 140 subjects does not impact the trial's principal objective or endpoints and maintains power of >90% (p-value < 0.01) for the primary endpoint of Moderate to Vigorous Physical Activity (MVPA) based on the effect size observed in Phase 2.

Following the evaluation of baseline MVPA characteristics, as measured by actigraphy, compliance to treatment and review of safety data of the randomized subjects in the ongoing Phase 3 REBUILD study, the trial's independent Data Monitoring Committee (DMC) supported reducing the target study size from 300 to 140 subjects.

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Early Phase Internal Exploration

Another way to use digital is to support early decision making about a drug

In early phase trials, the sample size for COA endpoints is often inadequate

This is because the study is powered on non-COA endpoints

eCOAs can offer insight into the patient relevant effect of the drug and help with go/no go decisions.

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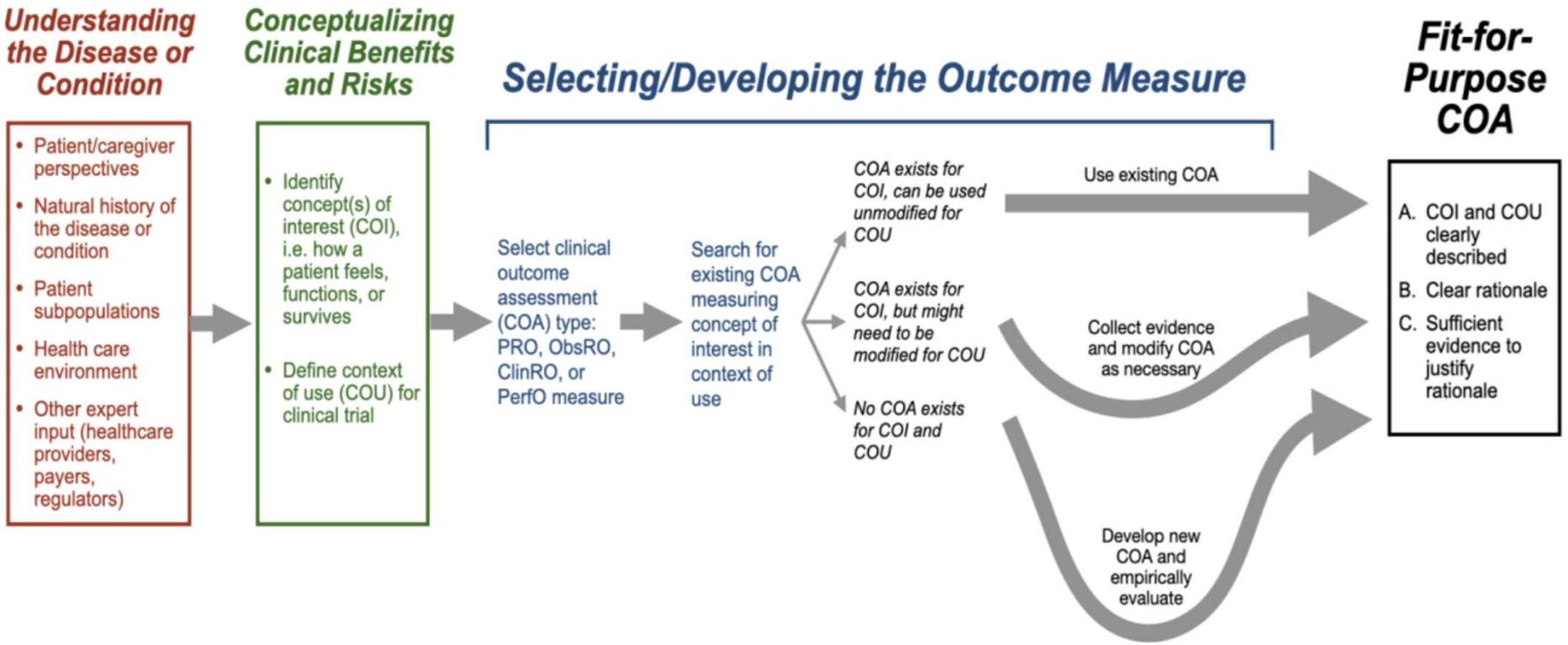
There is a process for defining and implementing a COA



Sources: Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for Purpose Clinical Outcome Assessments Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

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Develop measures that matter to patients

Meaningful Aspect of Health (MAH)

Aspect of a disease that a patient:

- does not want to become worse, or
- wants to improve, or
- wants to prevent

Concept of Interest (COI)

- Simplified or narrowed element that can be practically measured

Outcome to be measured

- The **measurable characteristic** influenced or affected by an individual's baseline state or an intervention
- This will be used to define an **endpoint** to be tested

Source: Manta C. et al

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Case examples: Measures that matter to patients with Parkinson’s Disease and Anxiety Disorder

	Meaningful Aspect of Health (MAH)	***Concept of Interest*** (COI)	***Outcome to be measured***
Parkinson’s Disease	“I want to be able to walk so I can carry my own groceries”	Activity (e.g., walking capacity)	**Outcome**: Walking bouts per day **Endpoint**: Percentage of patients with > 15% increase in activity monitoring from baseline Parkinson's
Anxiety Disorder	“I am exhausted and having trouble resting and relaxing”	Sleep (e.g. sleep duration)	**Outcome**: Time to sleep onset **Endpoint**: Average change in time to sleep onset one month from baseline

Source: *The Playbook*

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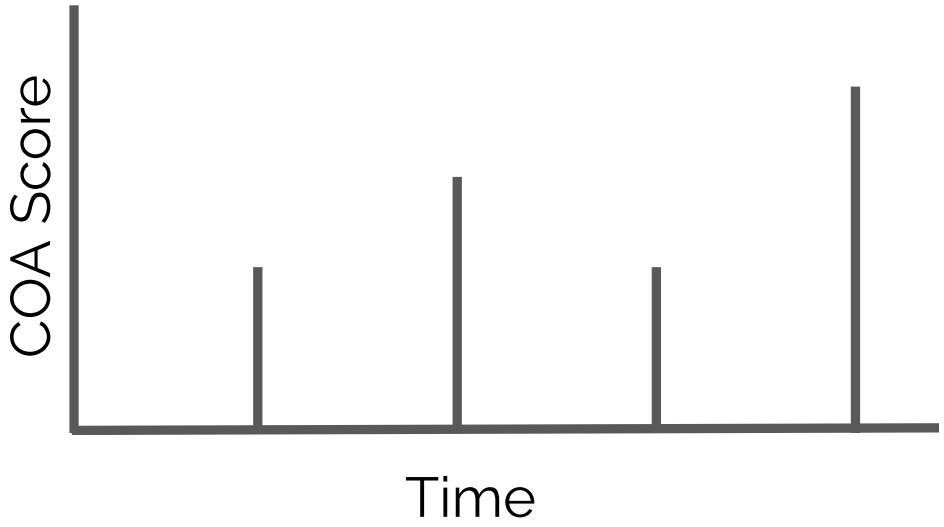
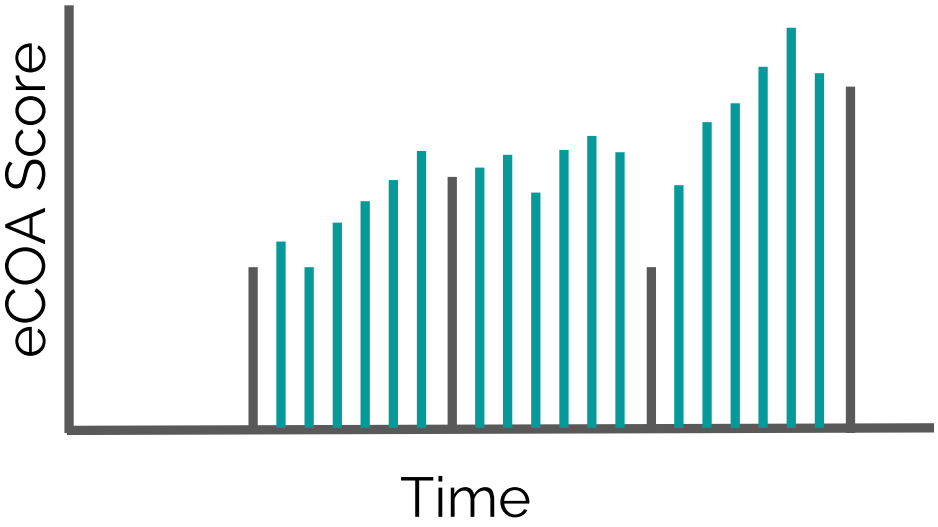
eCOA measurement leads to intensive longitudinal data





Traditional measurement may show a trend, but you miss the nuance

More frequent measurement accounts for fluctuations but leads to a lot of data

This can be useful, especially for things like time to event, and time to sustained event analyses

There are challenges to using this amount of data

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What methods can I use?

Traditional Methods

Existing methods such as MMRM can be used to analyse ILD

In these methods, a set of recordings can be summarized for each visit

- eg the mean of all data between clinic visits

This is a standard approach, but variability is being “hidden” from the model

Additionally, this variability could be important in its own right

Exploratory methods

ILD methods exist which incorporate the as collected data

These models, such as time series models, help to assess the within subject variability over time along with change trends for groups

ILD Models can account for things such as “weekend effects” by having a baseline day matched to a same treatment day (saturday-saturday)

These are not used as often and need Discussion and development with regulators

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