Setting meaningful PRO objectives in oncology clinical trials

Patient Focused Drug Development (PFDD) SIG: Hot Topics

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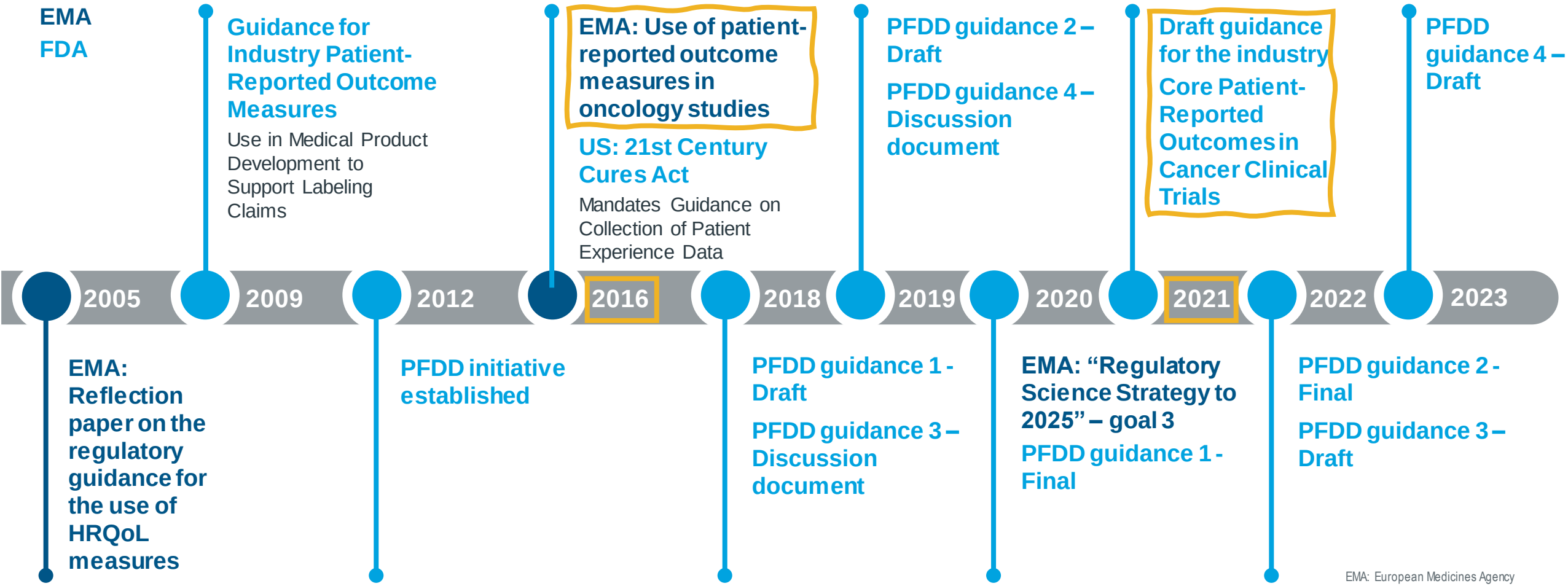
Towards patient centricity: Patient-Focused Drug Development (PFDD)



FDA Final PRO guidance 2009. Available at: https://www.fda.gov/media/77832/download
FDA Draft Core PRO guidance 2021. Available at: https://www.fda.gov/media/149994/download
FDA PFDD guidance 1-4 2018-2023. Available at: https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical
EMA PRO guidance 2005. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-regulatory-guidance-use-health-related-quality-life-hrql-measures-evaluation_en.pdf
EMA PRO guidance in oncology 2016 accessible at: https://www.ema.europa.eu/en/news/integrating-patients-views-clinical-studies-anticancer-medicines
https://www.ema.europa.eu/en/about-us/how-we-work/regulatory-science-strategy

EMA: European Medicines Agency
FDA: Food and Drug Administration
HRQoL: Health-Related Quality of Life
PFDD: Patient-Focused Drug Development
PRO: Patient-Reported Outcomes
US: United States

Oncology (and not only) trials are becoming patient-centric

- As per **FDA** Core Outcomes guidance[1] (2021) collect at least:
  - **Physical function (ability for physical effort)**
  - **Role function (ability to work and leisure)**
  - **Disease symptoms**
  - **Symptomatic side effects**
  - **Overall impact/bother from side effects**
- For **EMA**, **health status / Health Related Quality of Life (HRQoL)** has frequently been included in labelling.

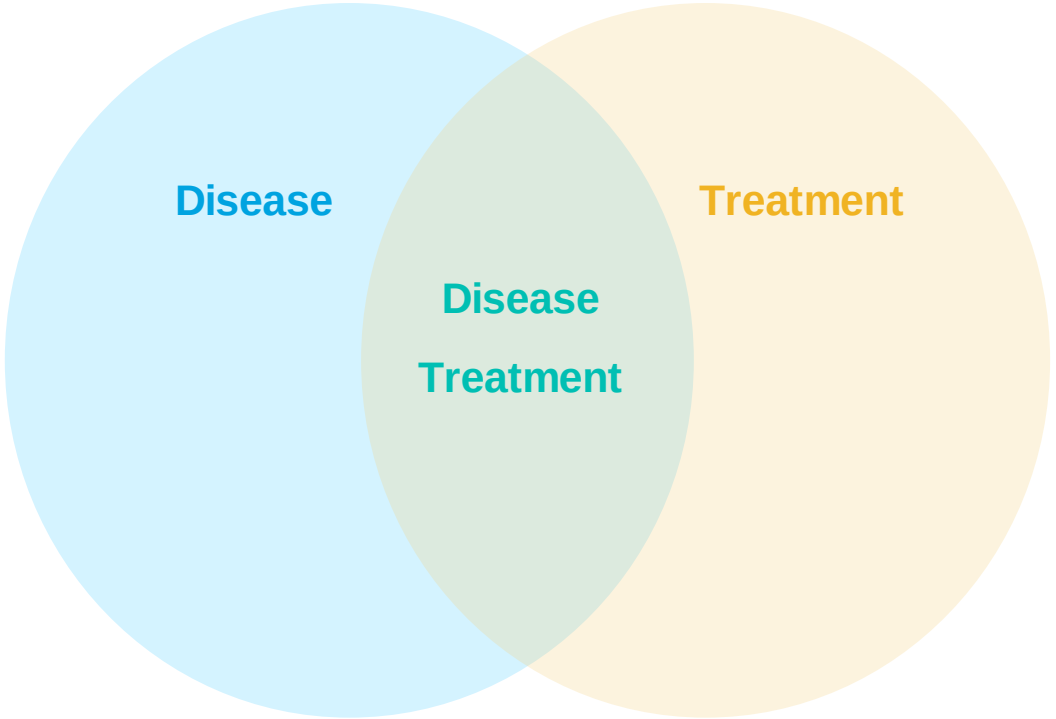
Patient-centric objectives can be efficacy or tolerability objectives

[1]Core Patient-Reported Outcomes in Cancer Clinical Trials: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/core-patient-reported-outcomes-cancer-clinical-trials

Efficacy and tolerability objectives may not be clearly distinguished

Qualitative work informs of symptoms of interest and if these are:

- Disease-related
- Treatment-related
- Disease- **or** treatment-related



Venn diagram based on IQVIA PCS: Using Patient Experience Data to Evaluate Medical Interventions Generating, understanding PED Book Chapter 3, Figure 1

[1]Core Patient-Reported Outcomes in Cancer Clinical Trials: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/core-patient-reported-outcomes-cancer-clinical-trials

PROs are increasingly collected in oncology and patient-centric objectives start climbing up in the hierarchy

Until recently

PROs all under one objective bullet in the **exploratory** list

Lately

Quite commonly all under one objective bullet in the **secondary** list

Currently

Several ongoing trials with *selected* PRO endpoints specified as **key secondary**

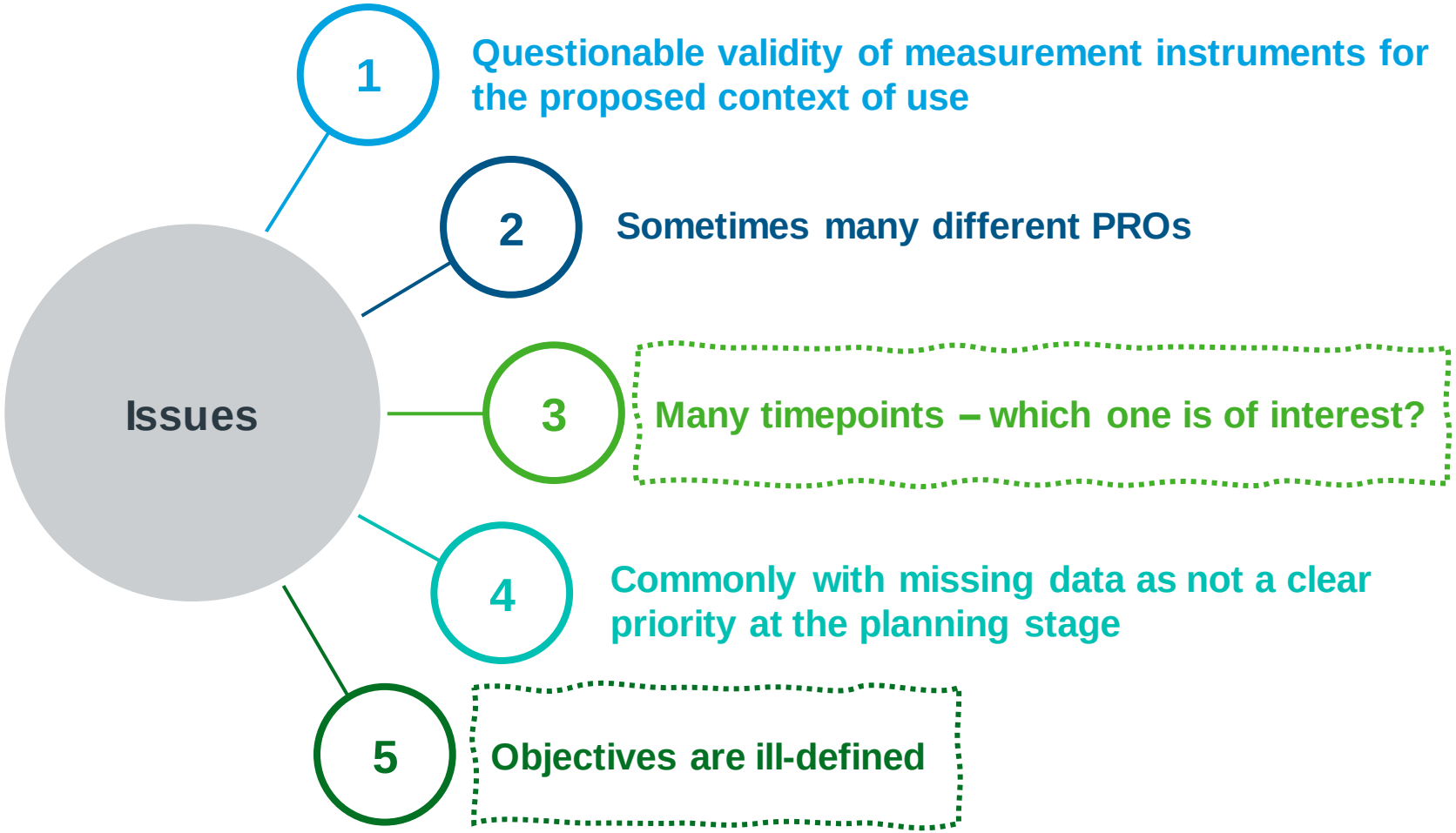
- Why? Not only because regulators say so
  - Demonstrating a benefit in HRQoL, functioning or symptoms is in line with patient centricity
  - Label claims have an obvious benefit to sponsors

Despite guidelines and general appetite, this does not translate to more PRO label language

	Indications approved	Included PRO data	PRO language included in EPAR	PRO language included in FDA label
2012-2016[1]	64	45 (70.3%)	21 (32.8%)	0
2017-2020[2]	128	100 (78.1%)	22 (17.2%)	Not in scope of review

[1]Gnanasakthy A et al A Review of Patient-Reported Outcomes Labeling for Oncology Drugs Approved by the FDA and the EMA (2012-2016). 22 (2019) 203 e209.
[2]Teixeira MM et al. A review of patient-reported outcomes used for regulatory approval of oncology medicinal products in the European Union between 2017 and 2020. doi: 10.3389/fmed.2022.968272. Accessed at: https://pubmed.ncbi.nlm.nih.gov/36035431/
Cella D et al 2022. Patient-reported outcomes labeling for oncology drugs: Multidisciplinary perspectives on current status and future directions. Accessed at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9634749/

Khadija Rantell concisely summarized the issues with PRO objectives and endpoints in last year's Conference (PSI 2023)



Instruments need to be reliable and valid, AKA measure what we want them to measure

Patient experience is multi-faceted by definition – what are we claiming?

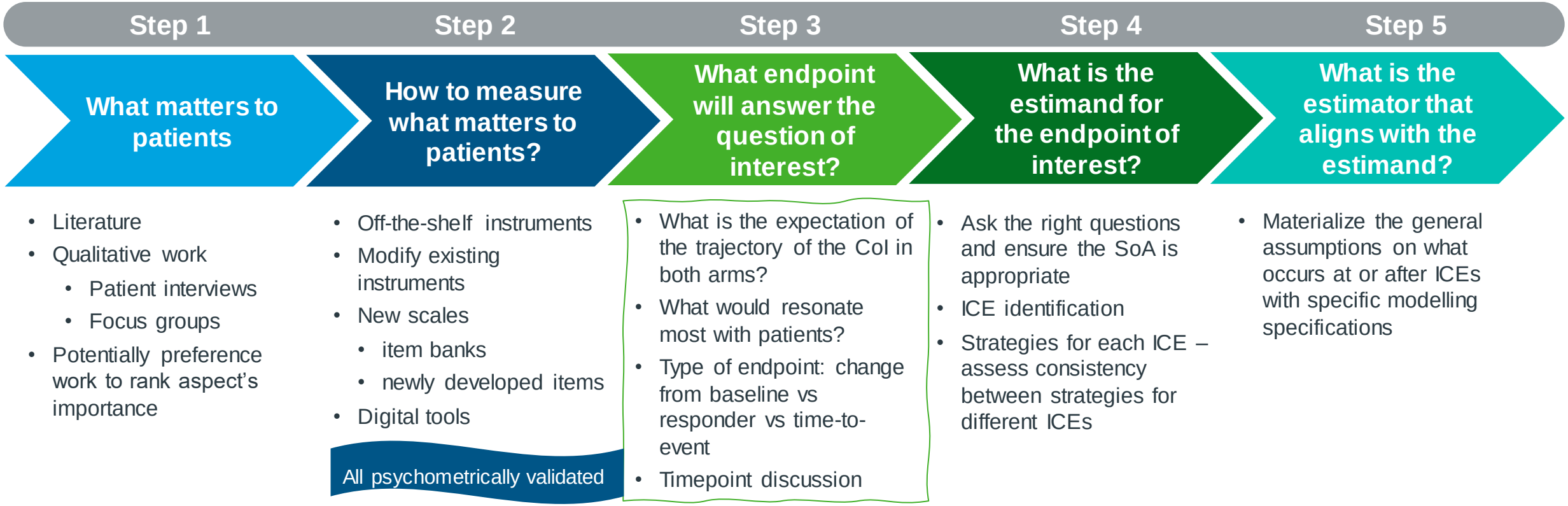
Patients are interested in the treatment experience throughout its course, not at month 6 only

Beyond technical issues and poor training/reinforcement of the importance of collecting these data, there are inevitable missing data due to the patient's condition

More in next slides

PSI 2023 Conference. Session: Importance of patient-reported outcomes in clinical studies: methodological challenges and future strategies. Skaltsa K, Rantell K, Schurmann C, Karu K, Aiyegbusi L

Process of constructing a COA/PRO endpoint: from concepts to claims



COA: Clinical Outcomes Assessments; CoI: Concept of Interest; HEOR: Health Economics and Outcomes Research
ICE: Intercurrent Events; PRO: Patient-Reported Outcomes

PROs reflect subjective judgement

- For **clinical objectives** in oncology, *clinical efficacy* questions are frequently straightforward and universally applicable (?):
  - How long will I survive?
  - How long will progression/metastasis be delayed?
  - Will the tumor shrink?
- For **patient experience**, questions will be subjective and differ from patient to patient, but also within the same patient depending on their position in the disease journey
  - E.g. for newly diagnosed patients, treatment-related symptoms may be a major concern, while for a later-line patient, a treatment with some level of toxicity may be acceptable if the hope for a survival benefit is the focus

What questions would a newly-diagnosed patient ask?

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Stay and listen to Devin Peipert in the next talk about tolerability

Non-comprehensive list of potential questions a patient may care about

- Will pain ease with treatment?
- **When** will it ease?
- Will it last? Will it persist even after this treatment stops?
- If I survive for another 2 years, will I be able to lead a normal life?
- Will I be able to do shopping and walk the dog **when I start treatment**?
- If not, **when** will I be able to do this **as I can now**?
- How long will I live **without experiencing severe symptoms** (i.e. with mild symptoms)?
- What adverse effects will I have? **How intense** will they be?
- **When** will they start? **When** will they stop?
- How many days will I be **not** experiencing side-effects (and be able to do daily tasks without problems)?

What are they really expecting from the trial?

What does the patient want to know?

- Improvement
- Early
- Sustained improvement
- Maintenance
- Accepting potential worsening, return to baseline
- If worsening, how long?
- Prepare for what is coming – will it be tolerable?
- Pattern of treatment-related symptoms

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We first listen, we then translate to technical language

Translating into PRO endpoints

- Change from baseline in pain at early assessments
- Time to first improvement
- Time to sustained improvement
- Change from baseline at 2 years
- Change from baseline in QoL/Physical or Role functioning at early assessments
- For patients with a worsening, time to return to baseline
- Time to severe symptom onset
- Descriptive analysis of symptom scores
- Descriptive analysis of symptom scores collected at a daily level

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Fixing a timepoint of interest: a historic regulatory practice

- Regulatory bodies are typically interested in **one pre-specified timepoint** for any claims sponsors make
- For clinical endpoints: **point of maximum therapeutic benefit**, e.g. response at month 30
  - → intermediate looks are typically **not** of interest

In settings where certain effects are expected when the therapeutic effect is achieved:

Aligning the timepoint of clinical and PRO endpoints may be sensible.

However, patient experience captures several aspects with different expectations. Patients may show:

- Increased treatment-related symptoms **at the beginning of the trial** affecting their HRQoL and functioning, e.g. nausea and vomiting, which may then cease
- **Immediate (and sustained?) improvement** in disease-related symptoms, e.g. cough in NSCLC
- Reach certain improvement **only after** the treatment effect is solidly reached, e.g. physical functioning after X months

Trajectories (horizontal look), rather than averages per visit (vertical look), may be of more interest

Step 3: Setting PRO objectives: timepoint of interest linking to endpoints

- If you are starting an oncology treatment – **what seems to matter most to you?**
  - **An early effect**, e.g. PF improvement 2 months after starting treatment allowing you to do the grocery asap?
  - **A late effect**, e.g. 2 years after the treatment, the tumor is likely to have shrunk and your PF improved as compared to BL
  - *"I would like a treatment that would **not make my PF worse** and ideally improve it from some point onwards"* → a wider horizon and all timepoints in between seem to be of interest
- **Time-to-event endpoints** aim to answer questions such as: **how long does it take until a worsening/improvement in PF occurs?**
- Regulators have expressed concerns due to incomplete and unequal follow-up between treatment arms, not collected data after treatment discontinuation, lack of standardization in the definitions (Fiero et al 2022)

"I would like to be able to do the grocery as soon as I start the treatment"

"It will be a tough time now, but hope I will be back to normal when treatment ends"

"Maintaining my quality of life seems a reasonable expectation"

It is the journey that matters, not the destination.

Fiero M et al 2022. Time to deterioration of symptoms or function using patient-reported outcomes in cancer trials. Lancet Oncol 2022; 23: e229–34
Reaney M and Raymond SA (2016): Therapeutic Success or Failure: A Journey, Not Just a Destination. Applied Clinical Trials 25 (2). Available at: https://www.appliedclinicaltrialsonline.com/view/therapeutic-success-or-failure-journey-not-just-destination.

Step 3: Setting PRO objectives

Current practice

- As with other outcomes, PRO endpoints are usually statistically defined as:
  - **Change from baseline** at timepoint X
  - **Responder** at timepoint X (responder defined based on a pre-defined threshold value considered as meaningful)
  - **Time to event**: e.g. time to worsening or improvement
- Flat "do all analyses for all domains" is an issue for all types of analyses – not everything is expected to follow the same trajectory
- However, this statistical categorization of a patient-level variable simplifies the questions we may be able to answer

- Uses original continuous scores, thus nice statistical properties
- Timepoint selection is an issue
- Missing data are an issue

- Relies on threshold definition – not so clear in oncology
- Poorer power

- Seems to be answering a relevant question
- Relies on threshold definition – not so clear in oncology
- Unequal follow-up is an issue (Fiero et al 2022)
- Definitions are not well thought of

How about starting from the question first?
Then define the patient-level variable, AKA endpoint

Fiero et al 2022 Time to deterioration of symptoms or function using patient-reported outcomes in cancer trials. DOI: 10.1016/S1470-2045(22)00021-3

Take away messages

On endpoints

- PFDD era: Oncology trials are becoming **patient-centric**
- **Qualitative work** asking patients *what* they care about, *when* and how this should be *ranked* will better inform endpoint construction
- There is still a lack of clarity on patient-centric objectives:
  - **Timepoint** for inference and consequent claim difficult to justify
  - **Journey probably matters most** – how do we capture this? Analyses aiming at describing *trajectories*, rather than averages at specific timepoints
  - **Time-to-event** have received interest *and* criticism – is there potential for using them more if more efforts are done for standardization?
  - **Not all aspects follow the same trajectory**: different analyses may be defined for different concepts

On analytics

- **Change from baseline is relevant:**
  - at **early** timepoints *and* at **later** timepoints
- **Time to event is conceptually meaningful - limitations noted**
  - Time-to-event endpoints need a thorough discussion on the right definition for each setting *and* aspect of interest
  - Time to **improvement** could be relevant for specific concepts, e.g. disease-related symptoms
  - Time to **worsening** could be a proxy for maintenance
  - For patients that experienced a worsening, **time from worsening to return to baseline levels** (+/- certain value) could be relevant
    - › could also be relevant for tolerability (see next session)

Thank you for attending!

For any questions, please reach out:

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