ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

PRO ASSESSMENT IN CANCER TRIALS

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oncology PRO
Educational Portal for Oncologists

DISCLOSURES

Emiliano Calvo has reported no conflicts of interest

Anita Margulies has reported no conflicts of interest

Eric Raymond has reported to be conducting research and has had consultancy activities for Eli Lilly, Pfizer, Novartis and Ipsen

Ian Tannock has reported no conflicts of interest

Nadia Harbeck has reported no conflicts of interest

Lonneke van de Poll-Franse has reported no conflicts of interest

SELECTING THE RIGHT PRO TOOL

Key Points

Review current thinking on patient-reported outcomes (PROs) in cancer clinical trials

Understand the importance of PROs (including Health-Related Quality of Life, HRQoL) as a measure of clinical benefit

Understand the feasibility and value of collecting PRO symptomatic adverse events in clinical trials

Describe the purpose and structure of the NCI PRO-CTCAE measurement system

WHAT ARE PATIENT REPORTED OUTCOMES?

PROs are reports about a patient's health condition that come directly from the patient

- Without interpretation or amendment of the patient's response by the healthcare team, partner or anyone else
- NB: multiple studies have shown that physicians and other health care professionals report symptoms differently to patients themselves

PROs are umbrella terms that includes

- Measures of symptoms } **Health Related Quality of Life (HRQoL)**
- Measures of functioning } **combines symptoms, functioning and QoL**
- Health status (Health Technology Assessment)
- Satisfaction etc.

DOCUMENTATION OF PROS

Paper and pencil

Digital capture (pc, tablet, smart phone)

- CAT: Computer Adaptive Testing (maximising measurement precision while minimising number of items to collect –minimising patient burden)

Interviewer administration (in person/telephone)

- Interviewer trained to use various assessment instruments
- Pay attention to avoiding interpretation or amendment by interviewer

PRO MEASURES/INSTRUMENT SELECTION

PROMs are the Measures or instruments used to measure PRO

When selecting (or developing) a PROM one needs to consider several methodological issues

- Validity (does it measure what it is intended to measure? Including cross-cultural validity that is important in international studies)
- Responsiveness/Sensitivity (sensitive to change or sensitive to differences between groups)
- Reliability (the ability of a measure to create reproducible results)

There is a variety of validated instruments to measure a specific type of PRO: Decide upon a decision-relevant outcome of interest. A conceptual model should provide the rationale for the PRO of interest

EXAMPLES OF VALIDATED PRO MEASURES

EORTC QLQ-C30 http://groups.eortc.be/qol/eortc-qlq-c30

- Measures QoL of cancer patients and is supplemented by disease specific modules (predominantly used in clinical trials)

FACIT http://www.facit.org/FACITOrg/Questionnaires

- Collection of QoL questionnaires (Including FACT)

PROMIS http://www.healthmeasures.net/explore-measurement-systems/promis

- Set of person-centred measures that evaluates and monitors physical, social and emotional health

PRO-CTCAE http://healthcaredelivery.cancer.gov/pro-ctcae

- Measures symptomatic toxicity in cancer patients (on clinical trials)

MINIMAL CLINICALLY IMPORTANT DIFFERENCE (MCID)

MCID: patient derived scores that reflect changes in a clinical outcome that are meaningful for the patient

Research by Osoba D, *et al.* (JCO 1998:16;139-144) suggests that for a normalised scale:

- 5-10% change is a small difference
- 10-20% is a moderate difference
- >20% is a large difference

- Thus a change of 10% in a normalised scale is a reasonable estimate of the MCID

MISSING DATA

- Most publications fail to describe the handling of missing data or discuss potential impact of missing data on findings
- Handling of missing data in statistical analyses received considerable attention in the literature and FDA and EMA have published guidelines

To remediate:

- Appoint and train dedicated personnel for data collection
- Promote completion in the most convenient way for patients (at home, on a tablet during hospital visits, online, paper, personal interview)
- Investigate reason for missing data: random influences or non-random and related to health status?

SELECTING THE RIGHT PRO TOOL

PRO measures should address a clinical trial research objective:

Efficacy: Does the drug provide superior improvement in disease-related symptoms or functional deficits?

- Pain, Total Symptom Score, Performance related outcomes
- Can support or negate a claim of treatment benefit

Safety/Tolerability: Describe the patient's experience while receiving anti-cancer therapy

- Patient-reported symptomatic toxicities

SELECTING THE RIGHT PRO TOOL

To assess efficacy in clinical trials

In trials evaluating treatment for people with incurable cancer, survival and its quality are the important endpoints. **A PRO should be a co-primary endpoint**

For trials of symptomatic patients select a minimal important change in a relevant PRO and measure the proportion of patients who achieve that change and for how long

In trials where many enrolled patients are asymptomatic time to deterioration endpoints can be utilised

Limitations of single arm or open-label trials in contemporary drug development

USING A PRO TOOL TO ASSESS EFFICACY IN CLINICAL TRIALS

PROs are properties of individual patients - there is little meaning to “average QoL”

In palliative trials patients will drop out – hence comparison of group means or medians will be misleading

Some patients will improve on therapy and some will deteriorate (just as some tumours will shrink and others will grow)

Hence measure changes in individual patients and describe the proportion entering each arm of the trial who satisfy a QoL response (or lack of deterioration) and how long it lasts

- This QoL response is analogous to tumour response (but much more meaningful)

PRO ASSESSMENT OF ADVERSE EVENTS:

Complementing existing safety assessments

Thoughtful incorporation of patients into cancer clinical trials is becoming a priority

- Assessing safety and tolerability with PRO measures can have utility across the drug development life cycle

The NCI PRO version of the CTC-AEs is a promising tool for this purpose

- PRO-CTCAE measures safety/tolerability, not efficacy
- Could provide well-defined descriptive PRO data to complement existing clinician reported safety data
- Significant work remains, but early adoption of PRO-CTCAE in commercial trials is underway

NCI's PRO VERSION OF THE CTC FOR AEs (PRO-CTCAE)

Implementing PRO-CTCAE in trials requires some resources

- Central coordinator effort and modest CRA effort
- PRO-CTCAE software available from NCI

Patient compliance rates very high

Interpretation and clinical utility of PRO-CTCAE is still evolving

Expanding adoption and implementation

- >100 adopters in 12 countries are testing it
- Collaborations with leading international organisations

NEW DEVELOPMENTS IN PRO ASSESSMENTS

Discussion about current use of (HR) QoL measures in cancer clinical trials as they include large, multi-domain assessments that attempt to evaluate a broad concept

FDA Criticism about ‘ static’ (HR) QoL measures that include the same questions, irrespective of stage or therapy being studied (Kluetz P, *et al*. AACR 2016):

- Increased flexibility can be obtained to adapt to differing disease and therapy contexts when measuring PRO-CTCAE in combination with physical functioning

EORTC advocates a combination of standardised (HR) QoL measures with validated items from item libraries like PRO-CTCAE, EORTC or other libraries

- This approach ensures evaluation of side effects and their impact on functional health problems reported by patients

Thank you!