Implementing PRO measures in clinical research and practice

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In the past 5 years I have received honoraria from:

- BMS, AZ, TEVA, NOVARTIS, EISAI, TAKEDA, PFIZER, LILLY, GENOMIC HEALTH, MYRIAD, NANOSTRING, ROCHE

Grant support from:

- BMS, GSK, MYRIAD, NOVARTIS

- I voted remain in the EU referendum
Benefits/harms of modern MBC treatment

• Advances in diagnostics, surgical & radiotherapy techniques, molecular biology and cytotoxic therapy

• More have a prospect of cure or surviving longer with their disease

• Considerable psychosocial and iatrogenic harms still created by diagnosis and treatment

• Both acute and long-term side-effects – latter not well understood as follow-up in trials short and few longer term ‘real-world’ data
In both research & practice HRQoL/PROs can:-

- Broaden parameters of benefit beyond DFS, PFS and OS
- Be useful prognostic indicators
- Aid decision-making
- Help determine supportive interventions needed and their efficacy
- Inform resource allocation, quality improvement and health-care policy
What patients and clinicians need to know for informed decision-making

• Most explanatory trials with stringent entry criteria mean we do not know enough about benefits, harms and burdens from patients’ perspectives or how they impact long-term survival

• More pragmatic trials with longer FU and deeper assessment needed to provide:
  - Better information about trajectory of important SEs -
    - when they start
    - if they ever improve
    - available ameliorative interventions and their efficacy

• More ‘real world’ studies would deliver even more information
PROs in Research

• Both FDA and EMA issued helpful guidance on PRO endpoints in clinical trials for drug approvals

• Both include clear criteria for label claims (some differences between FDA & EMA see Gnanasakthy et al, Value in Health, 2019)

• Requirements primarily focus on PROs to assess symptoms and side-effects

• Concordance between patient reported symptoms and physician reported woeful (see systematic review Atkinson et al, Supp.Care.Ca., 2016)

• NCI have developed PRO-CTCAE for items best evaluated by patient (https://healthcaredelivery.cancer.gov/pro-ctcae/)
Under-reporting of SEs using CTCAE grades

Toxicities shown below were all graded 0 by clinicians for >1000 breast & NSCLC pts in 3 RCTs having cisplatin +/- gemcitabine, rofecoxib, erlotinib, CMF and docetaxel (Di Maio et al, JCO, 2015)

- Aloepecia: 65.2%
- Diarrhoea: 50.8%
- Constipation: 69.3%
- Vomiting: 47.3%
- Nausea: 40.7%
- Anorexia: 74.4%
Barriers to PROMs in clinical practice

- Valuable aid for comprehensive clinical assessment but:
  - Still considerable resistance by HCPs to routine use of measures in clinic
    - Skepticism about the science and validity
    - Takes too long
    - Patients don’t like filling in forms
    - Unfamiliarity with the results and interpretation
    - Time and resources for implementation
- Plenty of systems available to link ePRO data with electronic health records
Computer Adaptive Testing (CAT)

• PROMs may need to be adapted to optimize measurement precision and relevance to individual patients whilst maintaining ability to compare score across studies

• Much psychometric work done using banks of validated items and computerized adaptive tests

• Requires factor analyses, item response theory calibration, simulation of measurement properties then appropriate software development to run

• See for example the EORTC CAT Core a computer adaptive version of the EORTC QLQ-C30 (Petersen et al, EJC, 2018)
Expanding assessment in MBC

• Many advances made in treatment that extend PFS and OS

• Are patients able to utilize this extra time or do SEs limit fulfilment of roles and responsibilities?

• Some may wish to continue working

• Have obligations to family and friends

• There is a societal cost if patients not able to function well
The Patient Roles & Responsibilities Scale (PRRS)

Stage 1
• Systematic review of existing PROMs validated in cancer patients (Catt et al, 2017)

Stage 2
• 2 qualitative interview studies informed scale development (Shilling et al, 2017)

Stage 3
• Preliminary evaluation and validation of new scale (Shilling et al, 2018)

Stage 4
• Further evaluation and validation in different study population

Comprises 16 core items in 3 subscales, identified with PCA in Stage 3:
1) Responsibilities & Social Life
2) Family Wellbeing
3) Financial Wellbeing
(Also standalone Jobs & Careers subscale)
Potential uses of PRRS

• Can be used with other applicable scales e.g. FACT-B-ES-AA-MAB etc in clinical treatment trials and intervention studies

• To aid clinical assessment (but still resistance by HCPs to using PROMs routinely in clinic)

• Many clinical interviews omit topics of deep concern to patients

• Some may have simple solutions or need referral to other HCPs/support services

• 4 ‘trigger items’ identified from PRRS which could be used to highlight areas in need of further discussion (a communication adaptive test)
Trigger items (Shilling et al, Qual Life Res, 2019)

• Combined data from 2 validation studies with 305 pts from mixed tumour sites

1. My illness interferes with performing my responsibilities at home (e.g. cooking, cleaning, gardening, DIY)

2. I worry about the impact of my illness on my children and/or other family members

3. I have difficulty meeting the additional costs of my illness

4. I worry that my illness will impact my employment in the future (including return to work)

• Correlations with the validation measures ranged from r=|0.36-0.69|
  • Trigger items are:-
Summary

• Not good enough to claim:-
  • a lack of understanding of data in area of measurement important to patients
  
• or that it takes too long to assess – doesn’t if correct measures chosen – eg PROMIS item library

• that patients don’t like filling in forms – most PROMs now available on variety of different platforms

• it can’t be implemented in clinical practice - many electronic systems for easy capture of PROs - but does need work on harmonisation

• regular monitoring is needed (part of the electronic record) not just in trials