PROMS in clinical trials may provide better information than CTCAE

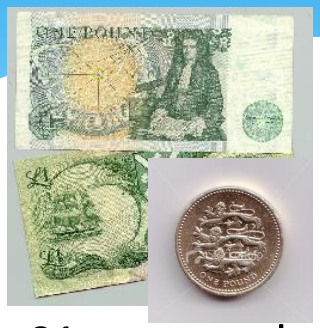
Lesley Fallowfield

SHORE-C

Sussex Health Outcomes Research & Education in Cancer

brighton and sussex medical school

Which year was this ?



£1 note replaced by coin

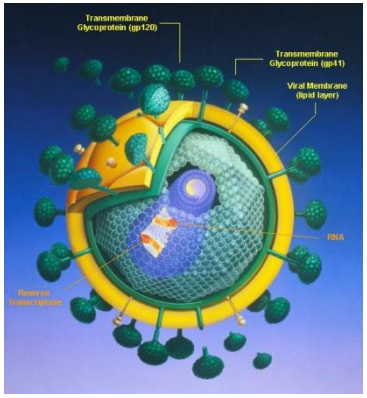
IRA bomb Thatcher's Cabinet at Grand Brighton

Torvil & Dean win Olympic gold

Lesley Fallowfield awarded DPhil joins Michael Baum's CRC Trials Centre at Kings

Miners strike over pit closures

Ist Apple Mac launched



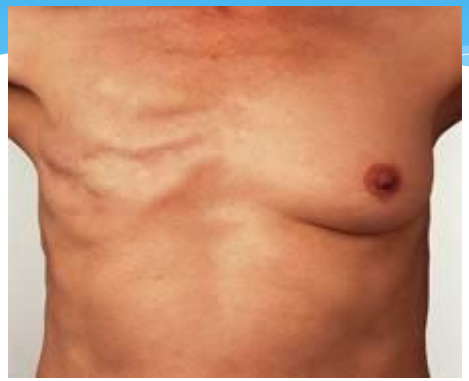
Aids virus identified

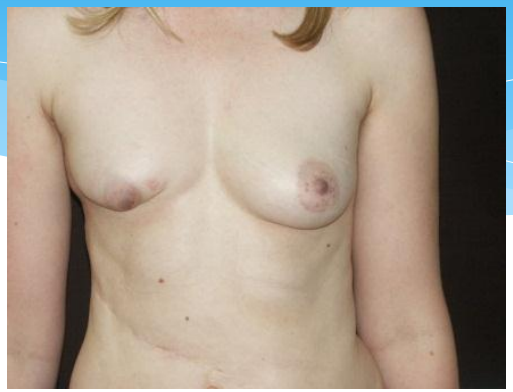
Treatment of breast cancer 1984

* mastectomy primary surgical treatment
* informed consent to trials arbitrary/cursory in many centres
* terms psycho-oncology, quality of life rare in medical journals
* only 11 papers published with words breast cancer and quality of life in abstract
* the few standardised, validated measures of PROs rarely utilised in clinical trials
* emphasis almost entirely on psychological morbidity

Mastectomy Vs Breast Conservation RCT

'A trial that everyone needed but nobody wanted'





- patients with EBC & no clear surgical treatment preference randomised to Mx or BC
- primary aim to establish safety of BC and test assumption would not produce unremitting psychological morbidity
- main trial failed to recruit but small psychosocial study completed (BMJ,1986, Fallowfield, Baum & Maguire)
- *No difference in anxiety, depression or sexual activity shown between groups*

Introduction

* many advancements and improvements made in cancer treatment in past 2 decades
* better imaging, surgical techniques, systemic therapies offer prospect of cure to many and longer lives for those with metastatic disease
* not all treatments are risk free
* discussion of therapeutic options must include discussion of harms and benefits
* includes appreciation of patient preferences about different devices and routes of administration

PROs assist in evaluation of therapeutic interventions

They :-

* broaden and complement parameters of benefit beyond response, DFS and OS
* are useful prognostic indicators
* aid decision-making
* help determine supportive interventions needed to accompany efficacious treatments
* inform resource allocation and health-care policy

Broadening parameters of benefit

* when palliation is the goal PROs arguably most important measure
* ‘complete responses’ rare in reports, more often ‘partial responses’ or ‘stable disease’
* these may excite clinical scientists but be of little value to patients experiencing troublesome side-effects of treatment
* sometimes there are no objective markers thus QoL may be the only criterion of benefit

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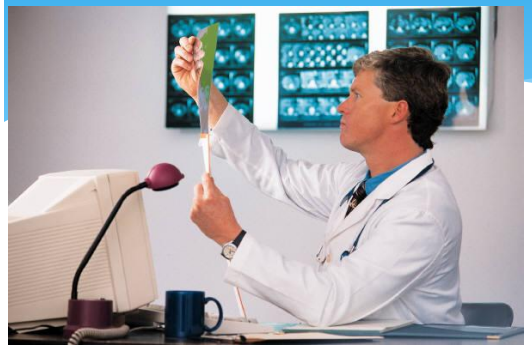
Patients and clinicians may have different values



- novel breast cancer treatments offer improved OS, PFS, DFS
- some also have unpleasant toxicities others serious side effects
- true benefits may be modest/uncertain due to limited follow-up
- desirable benefits and acceptable costs may differ between patients and HCPs

PROs may have prognostic or predictive value

considerable evidence from malignant melanoma, lung, breast, cervical, oesophageal, colorectal and bladder cancer that PROs are good prognostic indicators e.g:-

* QoL declines in patients ceasing to benefit from treatment before more orthodox measures **(Fraser et al, BJC, 1993)**
* QoL scores are stronger survival predictors than tumour size (CT scans) in colorectal patients with liver metastases **(Earlam et al, JCO,1996)**
* Baseline QoL a significant and independent predictor of loco-regional control in advanced H&N cancer **(Siddiqui et al, Int J Rad Onc Biol Phys 2008)**

Results from meta-analysis of 30 EORTC clinical trials (Quinten et al Lancet Onc.2009)

* baseline EORTC-QLQ-C30 data pooled from 10,108 pts across 11 cancer sites
* clinical parameters included age, gender, distant mets, performance status and site
* prognostic significance assessed using Cox proportional hazard models
* stratified multivariate model including sociodemographic, clinical and HRQoL parameters
  * physical functioning, pain and appetite loss provided significant prognostic information as did age, sex and distant mets
  * WHO performance status did not
  * adding HRQoL increased predictive accuracy of prognosis of OS by 6% relative to sociodemographic and clinical characteristics alone

Discussing treatment options and aiding decision making

* we can only tell patients about things that we have systematically studied and recorded
* initially most novel therapies appear to have better profiles than the standard treatment
* manner in which all adverse events and side effects collected not especially reliable
* several studies have shown that side effects are often underestimated

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Decisions patients face

* how much survival benefit is needed to trade off disadvantages and side-effects of treatment ?
* research suggesting patients accept toxicity for minimal benefits flawed
* if no clear survival benefits between treatments then QoL information crucial for decision-making

Do we have the data patients need for optimal decision-making ?

* veracity of many safety/side-effect data (mainly from trials) doubtful
* methods for collection and recording inadequate
* concordance between PROs & CRFs poor
* HCPs' toxicity assessments maybe more subjective

Symptoms of tamoxifen self report vs. published data (%)

symptom	interview self-report	published pt self-reports	published clin. reports
hot flushes	75	56-78	2-64
fatigue	47	61-72	0-26
sweats	36	47-55	11
loss of libido	31	22	0

(Fellowes et al, Br.Ca.Res.& Tmt, 2001, 66:73-81)

Typical Case Report Form

✓ Signs/Symptoms	NCIC-CTC Grade 1-4
☐ Nausea (GI NAU)	_____
☐ Vomiting (GI VOM)	_____
☐ Headaches (NE HEAD)	_____
☐ Hot flushes (EN FLA)	_____
☐ Vaginal bleeding (code as for GU HEM)	_____
☐ Visual disturbances (NE VIS)	_____
☐ Dizziness (NE DIZ)	_____
☐ Insomnia (NE INS)	_____
☐ Fatigue (FL LET)	_____
☐ Sweating (FL SWE)	_____
☐ Thrombo-embolic disease (CD VEN)	_____
☐ Other	_____

Symptoms are graded 1- 4 by clinicians according to severity

% tamoxifen symptoms rated ‘severe’ by women compared with clinicians’ report

Symptom	QoL(FACT-ES)	CRF (grade 3+)
hot flushes	38.2	3.6
weight gain	34.2	0
nights sweats	27.1	0.5
loss of libido	21.5	0
sleeping difficulties	19.2	0.4

Coombes et al, Proc. ASCO, 2003

Concordance of Reporting the Presence of Symptoms

* ES & CRF data stratified into categories comparing clinician with patient self reports of presence of endocrine symptoms

* Kappa stats used to measure degree of agreement

K=1	perfect agreement ****
K>0.8	good agreement ***
K<0.5	poor-fair agreement **
K=0	no better than chance *

Concordance of Symptom Reports of Any Severity (Coombes, 2003)

Symptoms	% Prevalence CRF	% Prevalence PRO	Kappa	95% CI
Hot flushes	49.8	73.5	0.73**	.70 - .75
Fatigue	21.0	71.5	0.72**	.41 - .47
Insomnia	17.9	69.4	0.45*	.42 - .48
Headaches	15.8	48.7	0.66**	.63 - .69
Dizziness	9.5	32.1	0.72**	.69 - .75
Vaginal bleeding	2.7	5.4	0.97***	.96 - .98

Concordance – clinician or proxy recorded v PROs

* in trials levels of symptom burden collected from PROs often higher than physician reported CTC **(Greimel, 2011)** and frequency and severity may differ **(Fallowfield, 2007)**

* little concordance between life threatening v. quality of life-threatening side-effects **(Savage et al, 2002, Fallowfield et al, 2004, Ruhstaller, 2009, Oberguggenberger, 2011)**

* toxicity assessments made by proxy raters provide different information from that provided by patients **(Basch et al, Lancet Onc, 2006)**

Why PROs may be more accurate than those on CRFs

* physicians reporting on CRFs often inaccurate, in busy clinics data may not be collected systematically
* focus is often on life-threatening adverse events so ascertainment bias
* leading, multiple questioning
* research nurses transferring medical records onto CRFs
* patients may fail to attribute SEs to treatment or be too embarrassed to mention some issues

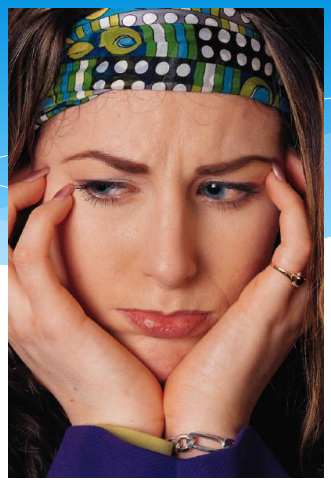
Other problems with summarising adverse events in cancer trials

* large amounts of AE data need to be summarised
* no uniform method for summarising key elements into concise statement of risk
* inability with CTCAE to summarise the severity of both acute and long-term toxicity (although some interesting new work reported) Trotti et al, 2007, Lancet Oncol)
* grading of severity of toxicity by doctors and research nurses highly variable

Common Terminology Criteria Adverse Events (CTCAE) v.4.02 (NIH, 2009)

* studies of investigational products demand toxicity assessment
* standardisation of data capture vital
* CTCAE empirically derived lexicon with grading categories 1(mild) to 5 (death related to AE)
* some of these are odd, rarely been subjected to reliability or validity testing

Diarrhoea:



“A disorder characterised by frequent and watery bowel movements”

breast cancer drugs reported to cause diarrhoea include:-

- capecitabine
- docetaxel
- paclitaxel
- lapatinib

Diarrhoea

1 Increase of <4 stools/day over bl; mild ↑ in ostomy output

2 >4-6 stools/day over bl; moderate ↑ in ostomy output

3 >7 stools/day over bl; incontinence, hospitalization indicated, severe ↑ in ostomy output limiting self-care ADL

4 Life-threatening consequences; urgent intervention indicated

5 Death

Loss of Libido:

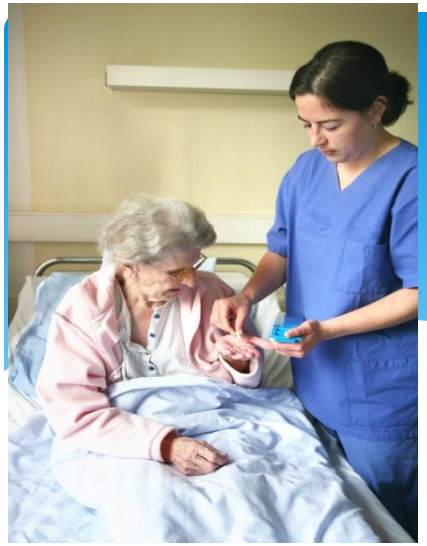
(classified under psychiatric problems)

“A disorder characterised by a decrease in sexual desire”

breast cancer drugs associated with loss of libido include chemotherapy and most of the aromatase inhibitors

Libido decrease

1	Decrease in sexual interest not adversely affecting relationship
2	Decrease in sexual interest adversely affecting relationship
3-5	No definitions/ratings



Nurses' assessments of advanced cancer patients

(Stromgren et al, 2001)

- patients' responses to 3 standardised PROMs compared with nursing notes
- 'Nurses Symptom Recognition' (NSR) % estimated
- previous study showed DSR low for all items except pain
- many unrecognised symptoms could be palliated

Item	NSR (%)
pain	84
physical function	84
nausea	64
vomiting	58
anorexia	41
dyspnoea	46
fatigue	36
sleeplessness	0
poor QoL	0

Proxy ratings patients/nurses in hospice care (To et al, 2012)

* Symptom Assessment Scale (SAS) 0-10 numerical rating scale for self-report of sleep, appetite, nausea, bowel function, breathing, fatigue and pain
* SAS completed weekly by patient and treating nurse
* Pearson's *r* showed poor – moderate correlations across all 7 domains
* nurses systematically under rather than over- reported symptoms especially appetite, nausea and fatigue
* proxy assessment even by experienced nurses poor surrogate for patient self-report

Why are there differences ?

* poor communication skills of HCPs eliciting information
  * leading & multiple questions
  * ascertainment bias

* reluctance of patients to admit to presence and/or severity of symptoms
  * fear treatment maybe stopped
  * embarrassment
  * no wish to appear ungrateful or complaining

Do we have the data patients need for optimal decision-making ?

* veracity of safety and side-effect data (mainly from trials) doubtful
* methods for collection and recording sometimes inadequate
* concordance between PROs and those collected by healthcare professionals poor
* agreement highest for observable symptoms e.g. vomiting, most discrepancy for non-observable e.g. fatigue and g.u. function (Basch et al, Lancet Onc, 2006)
* CTC assessments by HCPs more subjective than patients

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Where are we with PROs ?

* seem to be included in most RCTs
* rarely primary outcome
* not sure FDA or regulatory authorities ‘trust’ them although guidance has now been published
* in the past rarely used in labelling of products

EMEA

* PROs reported by patients- an umbrella term to cover single dimension and multi dimensional measures of symptoms, HRQoL, health status, adherence to treatment, satisfaction etc

* notion of multidimensionality key component – single domain cannot be considered as a basis for global HRQoL improvement in claims for label

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So which measures should we use ?

- obviously depends on the study but front runners:-
  - EORTC QLQ-C30 + modules
  - FACT-G + subscales
- new treatments
  - FACT-Taxanes
  - FACT-BRM Biological response modifiers
  - FACT-B+4 - Surgery aimed at preventing arm morbidity
  - FACT-ES Hormone therapy/Aromatase Inhibitors
- side effects
  - FACT-EGFRI-18,
  - FACIT-D for diarrhoea,
  - FACT-An for anaemia/fatigue,
  - FACT-BP for bone pain

PROMISing new initiatives

* NIH in US has funded the Patient Reported Outcomes Measurement Information System (PROMIS) (Garcia et al, JCO, 2007)
* large bank of items (questions mostly from standard HRQoL questionnaires) being compiled
* eventually this bank will be used in Computer Adaptive Testing (CAT)
* will permit more efficient, precise and psychometrically sound assessment

Ways forward - PRO-CTCAE (NCI)

* PRO-CTCAE has 81 patient reported items for clinical trials
* asks about presence or absence of symptom, frequency, severity and interference with usual activities
* recent survey (N=727) (Bruner et al, 2011)
  * 93% thought it useful for capturing patient reports of AEs and experiences during treatment
  * 88% it would improve completeness and 80% accuracy of data collection

FACT-B (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

Assessment

* many PROMs with good psychometric validity available
* challenge remains to get people to pay more than lip service to the results obtained
* and to help HCPs utilise results derived from assessments in clinic

"The times they are a'changing"

Time for research funders, regulatory authorities, heathcare professionals and payers to stop claiming:-

Physician reported = hard/objective

Patient reported = soft/subjective

Acknowledgements

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Sussex Health Outcomes Research & Education in Cancer