HealthSense
Registered Charity No 1003392

HealthSense Newsletter

for Science and Integrity in Healthcare

Issue 118, Spring 2022

Welcome to our first Newsletter as HealthSense!

As of January 2022, HealthSense became the new name for HealthWatch, the charity formed over 30 years ago to promote good science and integrity in healthcare. Our first issue as the *HealthSense Newsletter* includes a feature on our history, as well as articles by members new and old, and non-members, and experts and lay people. They share their experiences and expertise in promoting evidence. Since our beginnings as HealthWatch and now as HealthSense, our charity has had no salaried staff. Without external funding, we can be completely independent in challenging bad science.

Our News in Brief section features latest achievements and news from our brilliant volunteers, and opportunities to get involved. Let us know what you are doing to promote good science and integrity in healthcare by emailing newsletter@healthsense-uk.org

NEWS IN BRIEF

We have another namecheck in Private Eye

Challenging charities that promote unproven and potentially harmful treatments is painstaking work. HealthSense's Les Rose, a retired clinical scientist, has worked tirelessly for years checking claims and submitting reports, and now his efforts have been praised again by *Private Eye* after the Gerson Support Group (GSG) was removed from the charity regulators' list.

In the last two years Les had raised concerns with the Charity Commission about risks from Gerson's extreme diets, large doses of vitamins and coffee enemas. But the charity had failed to produce evidence for efficacy and safety of the treatments being promoted by Gerson practitioners to people affected by serious diseases including cancer.

As of 26 January 2022, the charity overview for Gerson Support Group now says "Removed charity". The Charity Commission, which regulates charities in England and Wales, issued a press release on 8 March stating "An organisation offering alternative therapies to people living with cancer has decided to wind up and be removed from the register of charities, after the Charity Commission challenged its public benefit … In response to the Commission's concerns, the organisation's trustees acknowledged that the evidence around Gerson nutritional therapy, and its claims to treat cancer and its symptoms, would not now meet the Commission's criteria for registration as a charity."

Following up on Les' work, *Private Eye* contacted the Charity Commission to ask why the GSG had been removed, and what happened to the £334,000 proceeds from the sale of the GSG's premises shortly before the charity was wound up. They were told that the charity had removed itself, its outstanding funds having been distributed to other charitable organisations, including two cancer charities subject to previous complaints. Both have supported Gerson therapy, and are allowed by the Charity Commission to continue operating. The regulator is said to be writing a case report, which we await with interest.

See Private Eye issue 1568 (4-17 Mar 2022), page 41

BMJ letter calls for retraction of trachea transplant research

A group of experts, including HealthSense member and 2003 award winner Peter Wilmshurst, have made a public call for removal of a highly publicised paper on a novel type of organ transplant research which has been linked to the deaths of several patients including two teenagers.

In: "Time to retract *Lancet* paper on tissue engineered trachea transplants" in *The BMJ* (2 March 2022), cardiologist Dr Wilmshurst and colleagues Leonid Schneider, Patricia Murray and Raphael Levy, explain how surgeon Paolo Macchiarini and his team claimed successful transplant of tissue-engineered airways in an article in *The Lancet* in 2008. Since then many of the claims made in the article have been found to be false, and Macchiarini was subsequently found guilty of research misconduct and received a prison sentence.

The 2008 paper, however, remains online and continues to advise future clinical care and research, despite calls for it to be retracted. See BMJ 2022;376:o498, and our report in HealthWatch Newsletter issue 109 (Summer 2019).

The 2022 HealthSense student prize competition for critical appraisal of clinical research protocols is open!

This year marks 20 years of our unique student prize competition, which rewards students of health care disciplines for honing their evidence-spotting skills. Since 2002, HealthSense has presented more than £20,000 in prizes of up to £500 each. Students compete by sizing up four short clinical trial protocols, and explaining which is likely to produce the most reliable evidence for the therapy it is testing, and why. The 2022 competition has just been launched for entries, with a closing date of 23:59 BST on Saturday 30 April 2022. Find out more about the competition and how to enter here.

In this issue:

News of the competition has been sent to all medical schools in the UK, but we would encourage HealthSense members to share with colleagues, friends and relatives to encourage entries.

We are extremely grateful to the Royal College of Surgeons of England for their generous sponsorship of this year's competition.

We've plans to take our work with students further, by putting together a toolkit of resources for self-learning evidence in health care, in a dedicated part of the new HealthSense website. Look out for this in the coming months.

Five-figure fine for unlawful advertising of a medical device

Our Australian partner organisation, Friends of Science in Medicine (FoSM), report a successful outcome to a complaint about an 'analgesic TENS system' marketed as the Healy.

The Therapeutic Goods Administration (TGA) has announced infringement notices totalling $26,640 issued to Sydney-based Healy World Australia Pty Ltd (Healy World) Healy World for an alleged breach of the Therapeutic Goods Act 1989. The Healy is a 'transcutaneous electrical nerve stimulation' (TENS) medical device, which was allegedly advertised with reference to a serious condition, with references to depression, anxiety and associated sleep disturbances, without the relevant regulatory permission.

HealthSense committee members Susan Bewley and Les Rose played a part by sending an Informed Opinion letter from HealthSense that was included with the FoSM complaint. Loretta Marron, CEO of FoSM, commented: "Considering the sums of money they have made, and continue to make, from vulnerable Australians, this is a small fine, but it makes a difference. The device continues to be listed as a TENS, hundreds of Healy 'partners' are still making claims on their websites and facebook pages, so there is still work to be done." The devices are also promoted in Europe.

New guidance for registering medical devices

The UK Medicines and Healthcare products Regulatory Authority (MHRA) has issued new guidance which says that all medical devices need to be registered with the MHRA before they are placed on the Great Britain market. This caught our eye because HealthSense recently responded to a public consultation on the subject. We have long been concerned by "bioresonance" devices which are widely promoted as health treatments (without good evidence) but have never had to register before. The guidance now says that, whatever disclaimers suppliers might issue, if they make medical claims then they are selling a medical device and must be registered.

Prince Charles book raises eyebrows

A provocative new book by HealthSense member and 2005 award winner Edzard Ernst has been getting favourable reviews. Charles, the Alternative Prince: An Unauthorized Biography follows the future monarch's passion for alternative medicine, reviews the evidence that the treatments he promotes do more good than harm, and finds it either weak or negative. Ernst is emeritus Professor of Complementary Medicine at the University of Exeter, and is a famous researcher and debunker of poorly evidenced alternative therapies. His book, which was published on 1 February 2022, has been praised on Medscape, Science-Based Medicine, and Psychology Today. Professor Ernst writes about his concerns over the Prince's advocacy in BMJ 2022;376:o310.

Latest publications

Female bodies and what we call them

Last September, an article on *The Lancet's* front cover referred to "bodies with vaginas", and it started a public discussion about the trend to remove sexed terms from discussions about female reproduction. Now a new Opinion piece co-authored by HealthSense chair Susan Bewley, sensitively explores the way we understand the language we use to describe pregnancy, birth, lactation, breastfeeding, and newborn care and the implications of change. The article invites open, thoughtful discussion on an often emotive topic.

Gribble KD et al. Effective Communication About Pregnancy, Birth, Lactation, Breastfeeding and Newborn Care: The Importance of Sexed Language. Front. Glob. Womens Health, 07 February 2022. https://www.frontiersin.org/articles/10.3389/fgwh.2022.818856/full

The *HealthSense Newsletter* welcomes news about HealthSense members' latest publications, please drop the editor a line at newsletter@healthsense-uk.org

POSTnotes: an opportunity for HealthSense experts?

An initiative of the UK Parliamentary Office of Science and Technology's research services, POST produces concise high quality evidence summaries for MPs on a variety of science and public health topics. It is possible to contribute to these summaries by suggesting literature, offering expertise or as a peer reviewer. The POST Work Programme page lists current topics and explains how to contribute if you have relevant expertise. HealthSense members include experts from a wide variety of fields, and this may be an opportunity for individuals to support the use of evidence in policy.

FEATURE

An early history of the charity now called HealthSense

By one of the charity's founder members, Professor Vincent Marks, with help from Caroline Richmond and an Afterword by our president Nick Ross. This is the story of the beginnings of HealthSense, the charity formerly known as HealthWatch

Vincent Marks

The idea of an organisation to counter health deception enacted through ignorance, malice or fraud was conceived one afternoon on 17 November 1987, *writes Vincent Marks*.

I had been attending a Royal Society of Health (RSH) Conference chaired by Professor Arnold Bender (1) at which I had delivered a talk on "non-hypoglycaemia" – a condition that had ravaged America in the 1960s and was currently gaining momentum in the UK.(2)

Contrary to what its name might suggest, non-hypoglycaemia is not related to diabetes and is a collection of diverse symptoms that might indicate anything, but most likely nothing, organic.

I immediately recognised Caroline Richmond as a kindred spirit. She was also on the programme and spoke on "Reporting of Food Hazards". We talked over lunch and I agreed to send her some literature relating to the National Council Against Health Fraud (NCAHF), an American organisation opposed to health misinformation, fraud and quackery, which I had belonged to since its foundation in 1983.

NCAHF was the amalgamation of three pre-existing organisations. The oldest of these was established by Stephen Barrett, born 1933 and a life-long opponent of quackery. He is still active despite the demise of NCAHF in 2011, following nine years of inactivity, and its replacement by *Consumer Health Digest*, a free weekly e-mail newsletter, which Barrett co-edits.

Strongly worded letters

Immediately after our RSH meeting Caroline Richmond, pictured below, received a strongly worded letter from the food journalist, Geoffrey Cannon who, though not at the meeting, requested that she cease attacking him and his views on food. I should mention that the views in question were ones of which, according to Caroline (and me), "most sane nutritionists strongly disapproved". One such nutritionist, Professor Arnold Bender, had in fact chaired the RSH meeting. He had apparently received a similar letter, though for some reason I did not.

Caroline Richmond

Following my letter enclosing information about NCAHF Caroline wrote to me on 23 November saying that she had been thinking "how to set up a similar body in Britain". She lost no time in doing so.

Concurrently with the birth of our idea, a manifesto appeared in the 1987 Christmas issue of the *BMJ* entitled "Fabric dyes: are they in the consumer's interest?" from the Dye Related Allergies Bureau (DRAB).(3) Their stated objective was the "wish to challenge the idea that fabric dyes are harmless…" and advanced arguments in favour of the concept that "although dyes in clothes are the cause of many medical conditions they have attracted little research interest".

The announcement was of course a spoof. A few lay people wrote to DRAB, to complain about one of its subsidiaries, the "Food Additives Research Team" (FART). The spoof's message was explained in a paper by Caroline Richmond a few pages later. She had written it after learning that permitted food additives are harmless despite being vilified by a number of individuals, and in the press, and on hearing of patients being exploited by private allergy practitioners prescribing expensive treatments for which there was absolutely no evidence of efficacy.

Total allergy syndrome

By a strange coincidence, some six years earlier, I had seen an unfortunate woman who had been diagnosed with a newly designated condition called 'Total Allergy Syndrome', and subsequently dubbed 'Twentieth Century Syndrome'. In this condition patients suffered from a variety of symptoms which were said to be due to allergies to everyday synthetic substances encountered in modern life. I saw this particular patient in consultation with Dr Jean Monro, one of the few medically qualified doctors who practiced "clinical ecology" in the UK. Monro had hoped to obtain dietary advice from me that might help her patient, Amanda Strang, but this was not my area of expertise and I was quite unable to help her or her patient. A more detailed account of Amanda Strang and total allergy syndrome appeared in *World Medicine*, edited by the late Michael O'Donnell, dated 20 March 1982, and a video of a short news report from earlier that year is on YouTube.

The exact origin of the term Total Allergy Syndrome is difficult to determine but it had been the subject of much press attention in Britain and the USA from about 1981 and was promoted mainly by surgeon Dr William Rea in America and Dr Monroe in the UK under the umbrella terms "clinical ecology" and/or "environmental medicine". It was the subject of research undertaken in Canada in 1984 that could find no organic cause for it and it has subsequently disappeared from scientific medical literature.(4)

In January 1988 Caroline drafted a proposal on "Why Britain Needs a Counter Quackery Organisation", which she sent to me and John Dobbing, Emeritus Professor of Child Growth and Development at the University of Manchester. He responded to Caroline's four-page draft at some length. The first point he made was that quackery and the fight against it was nothing new and he doubted that it was any more rife now than in the past. He suggested that we should take a "positive approach in the media towards denouncing charlatanry, such as neutralisation therapy, etc". He went on to say that "what is needed is a clearing house which journalists and the BBC could respect". This would consist largely of lay people "with access to a carefully chosen panel of doctors and other medical scientists". He further suggested that neither the BMA nor any other medical organisation would do this because the journalist would only say: "They would say that, wouldn't they?"

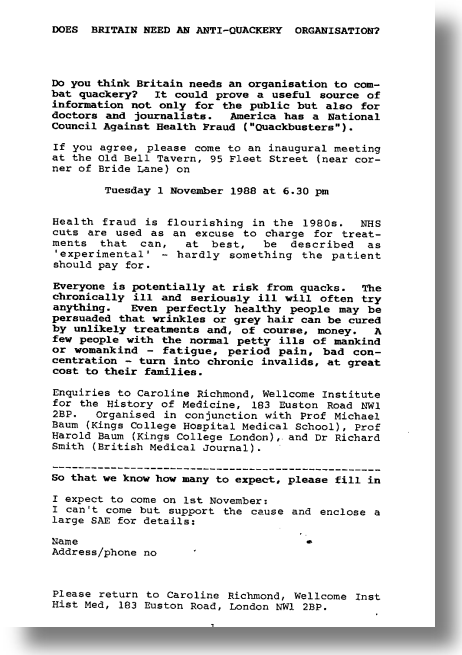
Caroline's own thoughts and reservations about setting up something like NCAHF were expressed in her letter of 23 November 1987 to the effect that "... it will need a minimum staff of 4: Admin/fund raising, investigator (her), lawyer and secretary". I must admit that I had given no thought to the organisational problems associated with setting up an organisation like NCAHF in this country and consequently we did nothing much more to advance the project, except think and talk about it to colleagues for the next nine months.

Early meetings

Caroline called a meeting at the Old Bell Pub in Fleet Street on November 1, 1988, to discuss whether Britain did need an anti-quackery organisation. It was attended by about 25 people, most of whom had either read about it in an announcement in the *BMJ* of 1 October 1988 or heard about it by word of mouth, mostly from Caroline herself. The group decided that there was a need and proceeded to elect Dr Oliver Gillie (then Health Editor on the *Independent*, and a

distinguished scientist and medical journalist) who had come to see what it was all about, as chair. A whip-round of those present raised enough money to pay the cost of hire of the room and a surplus of £7.00.

This was the working capital Dr Nick Beard, the newly elected treasurer, had to start the organisation, currently without a name but referred to as the Council Against Health Fraud (CAHF). Caroline agreed to act as secretary and a further meeting was arranged for 1 December 1988.



DOES BRITAIN NEED AN ANTI-QUACKERY ORGANISATION?

Do you think Britain needs an organisation to combat quackery? It could prove a useful source of information not only for the public but also for doctors and journalists. America has a National Council Against Health Fraud ("Quackbusters").

If you agree, please come to an inaugural meeting at the Old Bell Tavern, 95 Fleet Street (near corner of Bride Lane) on

Tuesday 1 November 1988 at 6.30 pm

Health fraud is flourishing in the 1980s. NHS cuts are used as an excuse to charge for treatments that can, at best, be described as 'experimental' - hardly something the patient should pay for.

Everyone is potentially at risk from quacks. The chronically ill and seriously ill will often try anything. Even perfectly healthy people may be persuaded that wrinkles or grey hair can be cured by unlikely treatments and, of course, money. A few people with the normal petty ills of mankind or womankind - fatigue, period pain, bad concentration - turn into chronic invalids, at great cost to their families.

Enquiries to Caroline Richmond, Wellcome Institute for the History of Medicine, 183 Euston Road NW1 2BP. Organised in conjunction with Prof Michael Baum (Kings College Hospital Medical School), Prof Harold Baum (Kings College London), and Dr Richard Smith (British Medical Journal).

So that we know how many to expect, please fill in

I expect to come on 1st November:
I can't come but support the cause and enclose a large SAE for details:

Name
Address/phone no

Please return to Caroline Richmond, Wellcome Inst Hist Med, 183 Euston Road, London NW1 2BP.

A meeting of the steering group was held at the Royal Society of Medicine in Wimpole Street, organised by Professor Michael Baum, a cancer specialist well known for his anti-quackery stance (and who thought the pub was a bit declassé).

At the next meeting, held at St Bartholomew's Medical College, Oliver Gillie resigned as chair and Michael Baum agreed to take his place until a permanent chair could be elected. The aims and name of the organisation were discussed at length without any decision being agreed.

We decided to have joint honorary presidents, one medical and one non-medical, and the names of various good and great people were put forward. Caroline Richmond and Michael Baum were delegated to consult and invite two suitable people from amongst those proposed.

Professor Baum had recently met Nick Ross the author, broadcaster, presenter of BBC's *CrimeWatch* and campaigner for evidence-based policy, and had invited him to meet some of his patients and see for himself the horrors inflicted by quackery. Nick was interested to help set up a campaigning group so he was invited, as was Dr Michael O'Donnell, editor of the unique and highly respected journal *World Medicine*. They both accepted nomination.

The nascent organisation started quack-busting without delay. A tip-off by an anonymous member had led to the 'defrocking' of a bogus doctor; then another member, David Pearson, reader in medicine at Manchester University, had pointed out dangerous and misleading errors in an article in the *Women's Journal*. In addition Professor John Garrow, the eminent nutritionist and later chair of HealthWatch, and I had individually complained to the BBC *Today* programme about "nutrition misinformation that included a bogus vitamin and perpetuation of the diet-hyperactivity myth."

Naming ourselves

A subcommittee was formed, chaired by journalist Mark Pownall, to produce a quarterly bulletin which barrister Diana Brahams would "read for libel and seek expert opinion on suspect matters". The bulletin, undated, duly appeared. It was the HealthWatch Newsletter.

The final meetings of the steering group were held at the Ciba Foundation in Portland Place which let it to the Campaign for a nominal fee. They led to the announcement, just five months after the inaugural meeting, of the Campaign Against Health Fraud (CAHF). The name itself was not finalised until 3 April and not without considerable debate as to the wisdom of using such a provocative title. It was immediately designated "Quackbusters" by the media.

At an early steering group meeting it was decided that "it would be unwise to invite practitioners using unproven treatments to join the steering group but that bona fide fringe practitioners would be welcome as ordinary members" – hence the acceptance, for example, of the late Dr George Lewith MRCP despite his opposition to much that CAHF stood for.

Another of the important determinations by the group was that it "would normally (be) desirable to accept only donations that came without attached decisions" and that "sponsorship, i.e., money with attached conditions, such as publicity for the donor, was unacceptable for the (organization's) general running, but would be accepted for particular activities, subject to prior discussions". Various charities had been approached for support without success. The Department of Health and Social Security had told Dr Mike Prophet, who had approached it on the committee's behalf, that "government support would normally be considered towards running costs of an organization (only) after they had already established themselves". Such help was never forthcoming.

The aims and constitution of the organization were drawn up and agreed upon at the last meeting of the steering committee. They were approved at its first Annual General Meeting on Wednesday 19 July 1989 with Caroline Richmond in the chair, having taken over from Mike Baum on 3 April that year.

Launch of HealthWatch

The formal launch, organized by *The Telegraph's* health writer Dr James Le Fanu, and Mark Pownall, was held at the Royal Society of Medicine on 8 May 1989. In the interim a number of financial decisions had been taken including the one to go ahead with the launch. This was despite the parlous state of finances which, on 6 February, consisted solely of membership fees and donations by members and stood at a measly £465.75.

The launch was accompanied by a press release entitled "Why a Campaign Against Health Fraud?" and attracted considerable media attention. It was preceded by a half-page article by James Le Fanu in *The Sunday Telegraph* of 7 May 1989. It was headed "Quackbusters v the Charlatans" and featured photographs of Caroline Richmond, captioned "disturbed by unproven ideas", and myself, captioned "Prof Marks: exposed rackets".

The launch itself was chaired by Caroline Richmond and introduced by Nick Ross. It featured talks by Professor Michael Baum, Professor John Garrow, Diana Brahams who was editor of the *Medico-Legal Journal*, and Dr Petr Skrabenek, Reader in Medicine at Trinity College Dublin and author, with James McCormick, of "Follies and Fallacies in Medicine" (Tarragon Press, Glasgow, 1989). Closing

comments were given by Dr Michael O'Donnell, co-president of CAHF and editor of *World Medicine*.

Media reaction

Not everyone greeted the launch of CAHF with enthusiasm. It had its detractors from the very start – but that is another story – as is the history of various campaigns that it fought and won (and very occasionally lost).

With the passage of time a number of members felt that the name Campaign against Health Fraud was too negative. This, together with the fact that the Charity Commissioners had indicated that they did not consider campaigns to be charitable, led the committee, by a majority vote, to propose a new name, HealthWatch. The proposed new name, together with several others, was put to the whole membership at its second AGM on 12 July 1990 and carried without dissent. The meeting agreed, also without dissent, to seek charitable status as HealthWatch. The treasurer, Michael Allen, gave a financial report which indicated that total expenditure for the year, £2,503.97, was more than met by members subscriptions. Donations and interest on deposits in the bank had led to an increase in assets from £1,225.19 in 1989 to £5,029,80 in 1990.

PHYSICIAN

GENERAL

Do we need the Quackbusters?

The Campaign against Health Fraud aims to protect the public from exploitation by fraudulent fringe practitioners — but it should beware of rejecting alternative therapies which do help some patients. Two doctors assess the value of alternative medicine.

The supply of misinformation

by Nick Beard

Through a successful marketing exercise, 'holistic' medicine has been hijacked by a loose coalition of charlatans, naive amateurs and misinformed medics. A holistic approach can mean many things. One meaning is of a sensitive awareness that illness has more than a purely physical basis — people *feel* bad. Real doctors know this — GPs could not do their jobs without this awareness.

Many fringe practitioners, in spite of their protestations of holism, uncarefully collude with the patient's desire to avoid facing the real roots of their psychosomatic problems. This is the other, dangerous version of 'holism' — a ragbag of half-truths sold to patients in an attempt to make a living out of alternative practice.

Worthless treatments

The Campaign Against Health Fraud was formed to fight such abuses with facts. There are two main aspects of its work. The first is to provide a network of expert opinion for those investigating fraud in healthcare. There have been successes already. Investigative journalist Duncan Campbell has made good use of our service in exposing the sale of worthless and dangerous combinations of milk powder and bacteria to HIV positive individuals. A fine example of alternative — untested and worthless — treatments being promoted in a realm in which one man's poison is another man's income.

The other activity of the campaign is an attempt to raise awareness of the need for medical research, and why would-be healers should not be believed until they cite good evidence to support their claims. Of course, there are problems with orthodoxy — we know this already. But unlike alternative practices, which do not evaluate their activities, orthodox medicine changes with research. Medical audit becomes ever more widespread. Treatments are replaced, changed, and dropped altogether, in the light of research. Such change does not occur as fast as many would like, but improvements do take place. There is, however, no reason for confidence that iridology will be discarded now research has consistently demonstrated its diagnostic uselessness.

No evidence

Thus an important criticism of alternative medicines is that there is almost no evidence that they work. Medical orthodoxy is accused of having double standards about this, as some orthodox treatments have not yet been subjected to rigorous trials. I believe this accusation to be unfounded.

> An important criticism of alternative medicines is that there is almost no evidence that they work

There are two types of evidence that a treatment works: confirmatory and supportive; the former being stronger evidence than the latter. Valid clinical trials are the surest route to confirmatory evidence, ideally using randomised, double-blind controlled methods. A double-blind trial compares an experimental remedy with a placebo — an inert substance. Neither the patient nor the medical assessor of the patient's progress know which preparation is being taken — it is double-blind. Patients are assigned to either the placebo or experimental group randomly, and large numbers are required to be sure

Nick Beard trained in medicine and is currently on sabbatical studying for an MSc in computing and knowledge-based systems. Richard Colman is a GP in York.

Physician November 1980

In subsequent discussions, during which it was pointed out that detractors of CAHF already believed it was "in the pay of the pharmaceutical industry", it was nevertheless agreed that the new HealthWatch would accept money "from any source, including the pharmaceutical industry" providing it was "given on a hands-off basis and providing no single interested party contributed more than 25% of CAHF's annual requirements". In reaching this decision we were influenced by Sir John Vane, Nobel Laureate, who pointed out that anyone contributing would do so because they had an interest and that this need not influence the behaviour of Healthwatch. [Editor's note: in the event, HealthWatch has never been offered nor accepted money from the pharmaceutical industry.]

When Caroline Richmond had been elected chair at the first AGM, John Garrow was vice chair. This was to change following the meeting of the executive on 14 August 1990, when Caroline resigned and John Garrow began his long term as chair of the organisation.

Professor Vincent Marks, Emeritus Professor of Clinical Biochemistry, University of Surrey, with contributions from Caroline Richmond, Medical Journalist and Author, London

Since 1990 ... Nick Ross continues the story

Nick Ross

In the early days, the charity HealthWatch was targeted specifically at charlatans who were preying on vulnerable patients, including those suffering from cancer.

But as more emerged about the extent of quackery and poorly-tested therapies, the aims quickly broadened to challenge all unproven 'cures' for illness, including those in orthodox medicine, and the charity's emphasis widened from being against bad treatment to being for high standards of evidence-based medicine and surgery. Accordingly, CAHF became HealthWatch in 1990.

Although HealthWatch grew in influence, it was a relatively small organisation and its name was never registered as a trade mark. Eventually, the NHS decided to pirate the name for "Healthwatch England", a new body established under the Health and Social Care Act 2012 which was effectively a committee of the Care Quality Commission, the organisation responsible for standard-setting in health and social care.

For several years the two organisations co-existed, and to some extent shared similar aims of quality control, but there was occasional confusion between the statutory body and the independent charity. The search began for a new badge that was similar yet distinct and which could be registered as a website and on social media, and HealthWatch formally re-registered with the Charity Commission as HealthSense at the end of 2021.

If the defining feature of a good name is that others seek to steal it, then HealthSense has a powerful heritage.

Nick Ross, Author, Broadcaster and Journalist, and President of HealthSense

Notes and references

1. The then Royal Society of Health is now the Royal Society of Public Health. Professor Bender was at the time its chair. He was the father of David Bender, who was for many years HealthWatch's secretary.
2. Referred to in the paper "Non-Hypoglycemia is an Epidemic Condition" NEJM; 1974:291:907-9 with an accompanying editorial by George Cahil
3. Richmond C. A newly discovered class of allergens: textile dyes? BMJ 1987;295:1596 and 1600-01 https://www.bmj.com/content/bmj/295/6613/1600.full.pdf
4. Stewart DE, Raskin J. Psychiatric assessment of patients with "20th-century disease" ("total allergy syndrome"). CMAJ Nov 1985;133(10):1001-1006

TREATMENTS

Why deny patients with chronic fatigue syndrome treatments that can help?

By Professor Peter White, responding to "It is not only drugs and devices that can harm" (HealthWatch Newsletter issue 114, Summer 2021)

Until I retired, a physician colleague and I jointly ran a clinic for people suffering from chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME). We looked after many patients who benefitted from cognitive behaviour therapy (CBT) and graded exercise therapy (GET).

So, it was more than disappointing to us when the National Institute of Health and Clinical Excellence (NICE) recently recommended that GET should no longer be offered (having wrongly said that it involved fixed increases in exercise) and qualified the use of CBT (only to be used to relieve distress, not fatigue itself).(1) It also perturbed four Royal Colleges of Medicine who responded: "Graded Exercise Therapy as defined in the guidance is not reflective of the personalised paced exercise programmes that are currently used in the NHS and termed GET. These have provided benefit to many patients and should not be discontinued." And "CBT remains a valuable treatment for alleviating symptoms in ME/CFS and services should ensure patients have access to this… ."(2) The new NICE guideline was also not approved by three CFS/ME clinicians who were members of the guideline committee; they resigned before publication.(3) A *Lancet* commentary was more critical: "In our view, this guideline denies patients treatments that could help them, undermines NICE as an international authority in guideline development, and jeopardises fundamental scientific principles by allowing some processes driven by ideology."(4)

Some of the reasons why NICE recommended that GET should no longer be offered were outlined by Caroline Struthers in her article in *HealthWatch Newsletter* 114, summer 2021, entitled "It is not only drugs and devices that can harm" .(5) Few would disagree with her point that we have not paid sufficient attention to the safety of psychosocial and behavioural interventions.(6)

But rather than refer to the potential harms of psychotherapies when used by people with mental illnesses, Caroline Struthers wrote about the safety of these treatments in people who don't have a mental illness – people with CFS/ME. As evidence, she criticised the largest trial of such treatments for CFS/ME – the PACE trial (which I helped to lead).(7) The trial found that CBT and GET were moderately effective and safe treatments, when added to specialist medical care, in comparison to two other treatments: specialist medical care by itself, and with additional adaptive pacing therapy (staying within the energy limits imposed by the illness).

A show trial?

Caroline Struthers asked whether PACE was a "show trial" – implying a verdict that was fixed before hearing the evidence. As evidence she noted that participants were told beforehand that CBT and GET were evidence-based, i.e., previous (smaller) trials had suggested that they worked. But research ethic committees rightly demand that researchers explain to patients the potential benefits and risks of any trial treatment. Having said that, we thought it important to see whether expectations influenced how well the treatments worked, and so built this into the trial design.(8)

We found that similar numbers of participants who were about to start either pacing therapy or GET were confident that it would help them, whereas the results showed that GET worked better than pacing therapy. In contrast, fewer participants were confident that CBT would help them, yet it worked as well as GET and better than pacing.(7) So, patients' expectations did not seem to determine how well the treatments worked – the verdict was not fixed beforehand. Caroline Struthers mentioned funding by the Department for Welfare and Pensions (DWP), which contributed £90,000 out of a total budget of nearly £5 million for the PACE trial, the major funders being the Medical Research Council (MRC) and Department of Health. But the DWP were not involved in any aspect of planning, delivery, analysis, or interpretation of the trial. And we reported that the numbers of patients receiving welfare benefits increased during the trial, with similar proportions between treatments.(9)

"Subjective" outcomes

A second concern of Caroline Struthers was that the trial was biased by using patient reported outcome measures (PROMs) as the primary outcomes, which might be influenced by participants knowing which treatment they had received, instead of using more objective outcomes, such as getting back to work.

We decided the best way of testing effectiveness was to ask patients to rate their own symptoms and how well they were functioning, something supported by others.(4) Who better to know whether these treatments work than patients themselves? As to whether using PROMs biased the results, we found that patients' expectations were unimportant (see above).(7) Additionally, a recent Cochrane systematic review suggested that using PROMs probably doesn't cause much bias.(10) We did report several objective measures, such as employment and benefits;(9) these treatments made no significant difference to the numbers working six months later, but there may have been alternative explanations for this, such as not having a job to return to.(9) The one objective measure to improve more after GET than comparison treatments was the distance walked in six minutes.(7)

Assessing recovery

Caroline Struthers pointed out that we changed the PACE trial criteria for determining who had fully recovered during the trial (because we thought they better reflected recovery), but it was not the case that "a participant could get worse on that measure during the trial, and still be classed as recovered at the end".(5) To be considered recovered participants had to meet not one but five separate measures of recovery, including rating their overall health as "much better" or "very much better".(11) The recovery rates were not the main findings of the trial; these were that the two primary outcomes of fatigue and physical function were both clearly better after both CBT and GET, when compared to either pacing therapy or medical care alone.(7)

Who should do research?

Caroline Struthers wrote that those who developed treatments should not undertake trials of them, suggesting that we would be conflicted and would want to show that they worked. But all three leaders of the PACE trial (and all six centre leaders) had personally led CFS/ME clinics and were motivated not by money or reputation, but by wanting to know which treatments work. Why would doctors want to give their own patients treatments that didn't work? And the trial design

allowed for treatments not to work; the analysis was done by a statistician who did not know which treatment was which (she was blind to treatment allocation). Social and other media are full of people promising cures for all manner of illnesses in return for money. In contrast, PACE trial treatment manuals are freely available for anyone to download.(12)

Are these treatments harmful?

Some patient self-help group surveys have found that many patients complain that both CBT and GET are harmful, particularly GET.(13) But there are problems with this evidence; we do not know whether survey respondents had CFS/ME,(14) and we don't know whether these patients received CBT and GET as they should be given.(15) Because of the concern about possible harm, we systematically measured six harmful outcomes in PACE and another more recent trial, such as reporting feeling worse, having side effects, or withdrawing from treatment.(7, 16, 17) We found that CBT and GET were just as safe as pacing or simply seeing a doctor.

Last year, following NICE's expressed concern about the harm of GET, we undertook a meta-analysis (analysis of all trial data combined) of three safety outcomes from the published trials of GET – feeling worse, withdrawing from treatment, and dropping out of trial follow-up.(18) We found no statistically significant differences in the numbers reporting feeling worse or stopping treatment prematurely, although we did find more patients dropped out of trial follow-up after GET (11%) than the control treatment (7%). We don't know why these patients dropped out, but this seemed to occur mainly in trials with high initial intensity of exercise.(18) It seems that GET is not harmful so long as it is delivered properly. NICE tried to move things forward by describing what they thought was a safer exercise programme,(1) but instead described something closer to pacing, which may not work.(7) But NICE was right to warn against undertaking exercise "such as telling them [patients] to go to the gym or exercise more";(1) in other words, don't do an exercise programme that is neither graded nor therapeutic.(12)

No long-term follow up?

Caroline Struthers complained about the lack of proper post-marketing surveillance for CBT and GET. But this is not the case. The PACE trial followed up patients until 2.5 years after they started their treatments and 18 months after the end of their participation in the trial – and found the effects of CBT and GET were maintained, with no evidence of harm related to receiving these treatments.(19) UK CFS/ME clinics have undertaken such surveillance several times, and these have suggested that these treatments do help some people, with no evidence of harm.(20-22) As is often the case, the limitation of these studies is that they were unable to follow up everybody, with outcome data available from between 51% and 78% in these studies; we have no certain way of knowing what happened to those who were missing.

PACE trial criticisms

The PACE trial has been criticised a lot over the years.(5, 23) These criticisms would be justified if the trial was either poor science or poorly conducted. Against these criticisms one might consider the following points: The trial was funded largely by the prestigious Medical Research Council, following peer reviews; a national ME patient charity helped to design and manage the trial; two independent oversight committees approved and monitored the trial; the trial results published in mainstream peer-reviewed journals, such as *The Lancet;*(7) and not one of the trial's twenty odd papers has been retracted following multiple complaints to journal editors. More detailed responses to these criticisms can be found on the trial website.(12) Regarding trial conduct, following a complaint to the Health Select committee, the independent Health Research Agency, which oversees all NHS research, concluded: "Our review suggests that the PACE trial exceeded expectations in its transparency when judged against contemporary expectations. … We have reviewed the concerns about conflicts of interest that were raised with me at the Committee and have found that the declarations were consistent with the contemporary standards. … We have therefore concluded that there are no regulatory concerns about the conduct of the investigators in relation to these issues."(24) Although no research trial can be perfect in every way, journal editors, funders, and independent oversight authorities continue to support PACE.

What is going on?

So, why has the PACE trial been so frequently criticised? It could be because it was the largest trial ever undertaken of these treatments, clearly showed the superiority of CBT and GET, and so is the most definitive trial published. Some people think that accepting that CBT and GET work implies that CFS/ME is either psychological (so explaining why therapy works) or due to being inactive (so exercise should help). But this is a misunderstanding; CBT and GET are also effective in reducing fatigue and improving function in many medical conditions, such as cancer, multiple sclerosis, arthritis, and lung diseases, where no one would suggest that these conditions are psychological. And we know that GET doesn't work by improving fitness. It seems to work by gradually removing the fear of engaging with usual everyday activities – gradually getting used to being active again.(25) And even if the PACE trial had never happened, the evidence from many other trials of these treatments still suggests that CBT and GET are the best available treatments.(26)

In conclusion, Caroline Struthers is right to underline the importance of assessing the safety of psychotherapies and rehabilitation therapies in general. But my concern is that treatments that are safe and help some people suffering from a life-changing chronic illness, for which there are no other effective treatments, should be available and recommended. In the end it is up to patients to decide whether they want to try a recommended treatment. But they won't be able to try it if it can't be offered.(4)

And what does this controversy tell us about the future, with many patients now suffering from chronic post-Covid fatigue and other symptoms? We need to properly diagnose these patients, researching into the different illnesses that make up "long Covid", and then test treatments that might help in the different groups of patients. For those with unexplained chronic fatigue, these treatments trials should include rehabilitation therapies, such as CBT and GET; then we will know whether these can help or not. And like in the PACE trial, outcomes should include: (subjective) ones that matter to patients (such as fatigue), ones that help us understand how a treatment works, and ones that measure harm.

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Disclosure

Professor White was one of the principal investigators of the PACE trial, is an independent member of the Independent Medical Experts Group, which advises the Ministry of Defence about its Armed Forces Compensation Scheme, and provides consultancy to the re-insurance company, Swiss Re.

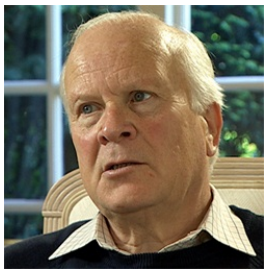
References

1. Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management. NICE 2021, NG206. https://www.nice.org.uk/guidance/ng206 (accessed 7 Feb 2022).
2. Royal College of Physicians, 2021. Medical leaders sign joint statement in response to NICE guidance on ME/CFS. https://www.rcplondon.ac.uk/news/medical-leaders-sign-joint-statement-response-nice-guidance-mecfs (accessed 7 Feb 2022).
3. Torjesen I. Exclusive: Four members of NICE's guideline committee on ME/CFS stand down. BMJ 2021; 374: n1937. doi: https://doi.org/10.1136/bmj.n1937
4. Flottorp SA, Brurberg KG, Fink P, Knoop H, Wyller VBB. New NICE guideline on chronic fatigue syndrome: more ideology than science? Lancet 2022; 399: 611-613, https://doi.org/10.1016/S0140-6736(22)00183-0
5. Struthers C. It is not only drugs and devices that can harm. HealthWatch Newsletter 2021; 114. https://www.healthsense-uk.org/publications/newsletter/newsletter-114/221-114-cbt-get.html?s=09
6. Nutt DJ, Sharpe M. Uncritical positive regard? Issues in the efficacy and safety of psychotherapy. Journal of Psychopharmacology. 2008 Jan;22(1):3-6. https://journals.sagepub.com/doi/pdf/10.1177/0269881107086283
7. White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet. 2011;377:823–36. https://doi.org/10.1016/S0140-6736(11)60096-2
8. White PD, Sharpe MC, Chalder T, DeCesare JC, Walwyn R ; PACE trial group (2007). Protocol for the PACE trial : a randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise, as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy. BioMed Central Neurology 2007, 7, 6. https://doi.org/10.1186/1471-2377-7-6
9. McCrone P, Sharpe M, Chalder T, et al. Adaptive Pacing, Cognitive Behaviour Therapy, Graded Exercise, and Specialist Medical Care for Chronic Fatigue Syndrome: A Cost-Effectiveness Analysis. PLoS ONE 2012 7(7): e40808. https://doi.org/10.1371/journal.pone.0040808
10. Moustgaard H, Clayton GL, Jones HE, et al. Impact of blinding on estimated treatment effects in randomised clinical trials: meta-epidemiological study. BMJ. 2020;368:l6802. https://doi.org/10.1136/bmj.l6802
11. White PD, Goldsmith K, Johnson AL, Chalder T, Sharpe M. Recovery from chronic fatigue syndrome after treatments given in the PACE trial. Psychological medicine. 2013 Oct;43(10):2227-35. https://dx.doi.org/10.1017%2FS0033291713000020
12. PACE Trial website. https://www.qmul.ac.uk/wiph/centres/centre-for-psychiatry-and-mental-health/research/pace-trial/ (Accessed 11th Feb 2022)
13. Kindlon T. Do graded activity therapies cause harm in chronic fatigue syndrome? Journal of Health Psychology 2017; 22: 1146–1154. DOI: 10.1177/1359105317697323
14. Brimmer DJ, Maloney E, Devlin R, et al., A pilot registry of unexplained fatiguing illnesses and chronic fatigue syndrome, BMC Res. Notes 6 (2013) 309. https://doi.org/10.1186/1756-0500-6-309
15. Gladwell PW, Pheby D, Rodriguez T, Poland F. Use of an online survey to explore positive and negative outcomes of rehabilitation for people with CFS/ME. Disabil Rehab. 2014;36:387-94. https://doi.org/10.3109/09638288.2013.797508
16. Dougall D, Johnson A, Goldsmith K, Sharpe M, Angus B, Chalder T, White P. Adverse events and deterioration reported by participants in the PACE trial of therapies for chronic fatigue syndrome. J Psychosom Res. 2014;77:20-26. DOI: https://doi.org/10.1016/j.jpsychores.2014.04.002
17. Clark LV, Pesola F, Thomas JM, Vergara-Williamson M, Beynon M, White PD. Graded exercise therapy guided self-help versus specialist medical care for chronic fatigue syndrome (GETSET): a randomised controlled trial. Lancet. 2017;390:363–73. https://doi.org/10.1016/S0140-6736(16)32589-2
18. White PD, Etherington J. Adverse outcomes in trials of graded exercise therapy for adult patients with chronic fatigue syndrome. Journal of Psychosomatic Research 2021; 147: 110533. https://doi.org/10.1016/j.jpsychores.2021.110533
19. Sharpe M, Goldsmith KA, Johnson AL, et al. Rehabilitative treatments for chronic fatigue syndrome: long-term follow-up from the PACE trial. Lancet Psychiatry 2015; 2: 1067–74. https://doi.org/10.1016/S2215-0366(15)00317-X
20. Crawley E, Collin SM, White PD, et al. CFS/ME National Outcomes Database, Treatment outcome in adults with chronic fatigue syndrome: a prospective study in England based on the CFS/ME National Outcomes Database, QJM: An International Journal of Medicine, Volume 106, Issue 6, June 2013, Pages 555–565, https://doi.org/10.1093/qjmed/hct061
21. Adamson, J, Ali, S, Santhouse, A, Wessely, S, Chalder, T. Cognitive behavioural therapy for chronic fatigue and chronic fatigue syndrome: outcomes from a specialist clinic in the UK. J R Soc Med 2020; 113: 394–402. https://doi.org/10.1177%2F0141076820951545
22. Smakowski A, Adamson J, Turner T, Chalder T. (2021) Graded exercise therapy for patients with chronic fatigue syndrome in secondary care – a benchmarking study, Disability and Rehabilitation 2021, https://doi.org/10.1080/09638288.2021.1949049
23. Patients' power and PACE. Lancet 2011; 377: 1808, May 28. https://www.thelancet.com/journals/lancet/issue/vol377no9780/PIIS0140-6736(11)X6022-1
24. Montgomery J. The PACE trial and the Committee's inquiry on Research Integrity. 2019. Available on: https://www.parliament.uk/documents/commons-committees/science-technology/Correspondence/190129-Sir-Jonathan-Montgomery-Health-Research-Authority-to-Chair-re-PACE-trial.pdf (last accessed Feb 7th, 2022)
25. Chalder T, Goldsmith KA, White PD, Sharpe M, Pickles AR. Rehabilitative therapies for chronic fatigue syndrome: a secondary mediation analysis of the PACE trial. The Lancet Psychiatry 2015; 2: 141-152 , http://dx.doi.org/10.1016/S2215-0366(14)00069-8
26. Sharpe M, Chalder T, White P. Evidence-Based Care for People with Chronic Fatigue Syndrome and Myalgic Encephalomyelitis. J Gen Intern Med 2022; 37, 449–452. https://doi.org/10.1007/s11606-021-07188-4

MEETING REPORT

A new approach to screening for cancer

A surrogate endpoints workshop at a recent Cancer Research UK conference prompts a new approach to screening. By Michael Baum, with an introduction by Mandy Payne



Michael Baum

Introduction

In clinical trials, a surrogate endpoint (or surrogate marker) is a measurable effect that might be linked to a real clinical outcome – but the link is not necessarily guaranteed. For example, eating a diet high in fatty foods might be linked with likelihood of death by heart attack, so a trial might use "intake of fatty foods" as a surrogate marker for "risk of death by heart attack", because the former is very much easier to measure in practice.

Surrogates are attractive to study, because their changes can often be detected early, even when the clinical outcome of interest may be long-term like deferred death or relapse.

The drawback is that the link between the surrogate and the clinical outcome may not be real, or may be part of a more complex picture. So, trial evidence gained from use of a surrogate marker may not be reliable – association does not mean causation.

The question of surrogates is topical with talk of new blood tests that claim to be able to screen for many different cancers – so-called "liquid biopsies". There are concerns that these could generate harms, for example through false positive results leading to anxiety and unnecessary treatment. Also, that calls for "blood tests for cancer" are driven more by commercial interests than the prospect of patient benefit.

A Screening Surrogate Endpoints Workshop was part of Cancer Research UK's virtual "Early Detection of Cancer Conference 2021", held 6-8 October last year. It was attended by HealthSense chair Susan Bewley, and our longstanding member the top breast cancer surgeon and researcher and 2002 HealthWatch Award winner, Michael Baum.

Susan was pleased to see that so many of the academics gathered from all over the world (some Americans getting up at 4.30am to join in) had concerns that HealthSense shares about the potential harms of using surrogate endpoints. But she had the impression that some speakers were not really listening. "Dr Peter Sasieni's comment that '50% of us are going to get cancer' was, I felt, seriously scare-mongering and unworthy," said Susan. "So what? 100% of us are going to die of something."

Michael Baum was there because he had chaired the national committee on PSA screening for prostate cancer, and for his experience running randomised controlled trials and his understanding of the hazards of surrogate outcomes.

"I was so provoked by the not-so-hidden agenda, that I spent the next day writing the following suggestions on how we might progress," Mike said. "What I think about liquid biopsy and screening for multiple cancers is written between the lines. Their uncritical approach also suggests a total ignorance of the natural history of sub-clinical cancer."

Re-thinking approaches for screening

Michael Baum writes: In my opinion, we have enough evidence to abort screening programmes using PSA tests for prostate cancer (1) and to close down the NHS mammographic screening programme for breast cancer.(2,3)

Yet, I don't want to appear a nihilist and would like to offer some suggestions that could help in rethinking approaches for screening following a biopsy diagnosis of a "solid" tumour. I have no opinions about screening for signs of cancer in the blood and await with interest the workshop's report of screening for multiple cancers following "liquid" biopsy.

- Screening theory is based on the assumption that cancer progresses according to a linear or logarithmic trajectory, shedding cells that nest in distant niches that then progress according to a log-linear dynamic. I think that is highly unlikely for most solid tumours. The natural history of these cancers can better be explained using non-linear mathematics - chaos theory. Imagine microscopic disease foci that exist in a state of dynamic equilibrium that can be perturbed one way to progress or the other way to regress.(4,5) I believe that we can make use of this model in planning new randomised controlled trials (RCTs), see below.
- The next thing to consider is that improvements in therapy over the last 20 years have narrowed the window of opportunity for screening. For example, at the time breast cancer screening trials were launched, 5-year survival was 50%. Nowadays it is 90%. Furthermore, breast cancer has now been relegated to number 7 in the league table of causes of death for women. Deaths from ischaemic heart disease or strokes are far more common. The corollary to this is that to show say, an improvement of 10% in cause-specific mortality, the number of people that would have to be screened in order to detect this improvement would be huge and require multi-national support.(6) (See also the Appendix at the end of this article with a quote from IBIS II trial.)
- Much concern was expressed during the workshop that the improvements in therapy during the recruitment and follow up of the trial would incur biases. I beg to differ. In a big pragmatic trial, women in both arms of the trial would receive the "standard of care" in the community at large.
- There was a lot of discussion about the cellular and molecular biology of each cancer that might require multiple trials measuring multiple surrogate markers. I find that hard to believe and much harder to implement, but I see a way around it. First of all, there needs to be *a priori* hypotheses clearly stating why a certain profile of a certain tumour might behave differently in a screening trial. Otherwise, you go on a fishing expedition. The large pragmatic RCTs I envisage should have the capacity of building up an archive of tumour samples stored at -70^0 These specimens would be available for exploring the relationships between cancer biology and "early diagnosis". This has already been achieved in the ProtecT trial of prostate cancer screening (1) and the ATAC trial comparing treatments for early breast cancer.(7)

I believe there is a way to exploit the alternative mathematical model for the natural history of cancer. It could provide a useful surrogate endpoint for cause-specific mortality, as well as indicate the absolute benefits for subgroups of patients pre-determined by defined cellular and molecular biology of the cancers. It uses "hazard rates".

Hazard Rates

A hazard rate plot is a simple graph that describes the percentage chance of an event – in the case of cancer, this might be risk of tumour recurrence – over each period of observation from time zero. The periods for each observation are, conventionally, year on year. If the hazard rate were constant for individual patients, you might expect a parabolic curve with an average flat peak in the median period follow up (see the yellow line in Figure 1). But in fact, irrespective of grade or stage of disease at the time of detection, the peak hazard rate is at +/- 2 years (blue lines).

The prognosis of the patient is reflected by the height of the peak rather than the timing.(8,9,10) (Incidentally, this is indirect evidence that the trauma of surgical intervention kickstarts clones of latent disease at distant sites.(4))

These two figures illustrate what I've just described:

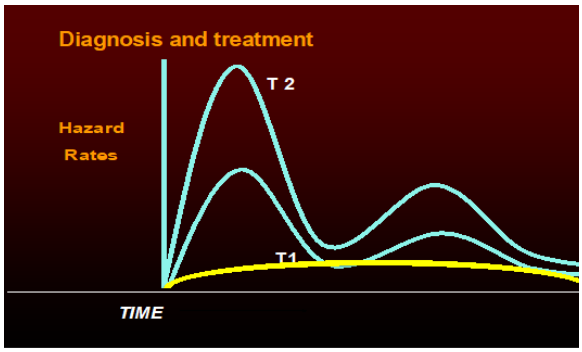


Figure 1. An illustration of pattern for hazard rates following diagnosis and start of treatment for cancer.

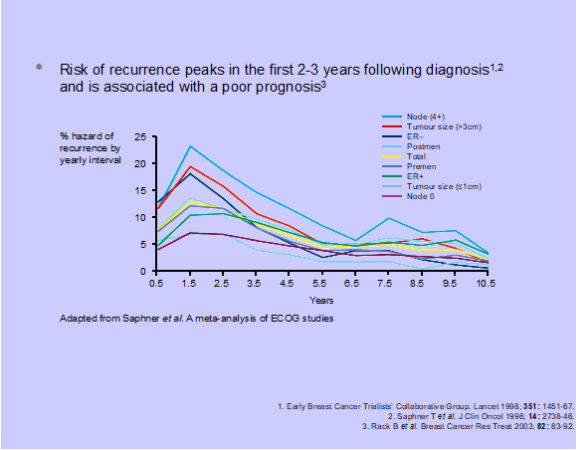


Figure 2. Percentage risk of recurrence over the years following diagnosis.

Armed with these ideas I can foresee the design of a large pragmatic trial that is realistic yet might answer some of the questions thrown up by the workshop.

A design for a "meta-trial"

To generate reliable evidence the trial must be very large and therefore multinational. Here I'm talking about multiples of 10,000. This is not impossible – the ProtecT (1) trial recruited about 250,000 in the UK alone. To achieve these numbers, we need to be practical and spread the net wide. When cancers appear in the screened and control arms, the stage and grade of disease are reported, and biopsy specimens are stored in an archive for genetic information in due course. Deaths from breast cancer will be reported and, with a large enough trial, we might be able to look at rate of deaths from all causes too. I would argue hard for the latter because over-diagnosis of potential early cancer can lead to over-treatment that can result in deaths from the toxicity of treatment.

This is illustrated by infographics such as this one from the Harding Center for Risk Literacy describing the outcome of mammographic screening:

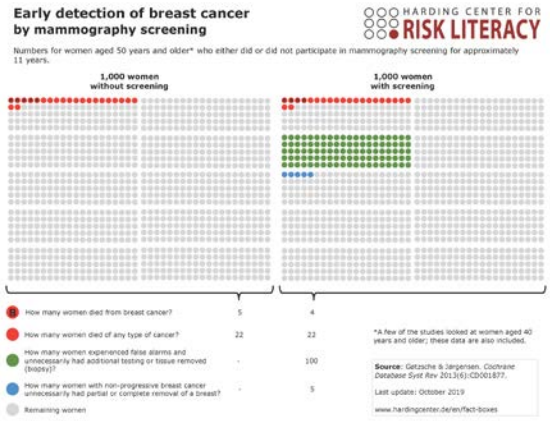


Figure 3. Icon array diagram illustrating risks with or without mammographic screening. Red dots represent cancer deaths. Green and blue dots in screened group represent harms from false alarms and unnecessary tests and biopsies (green) and unnecessary partial or complete mastectomy (blue). © Harding Center for Risk Literacy.

Furthermore, we need to measure psychological impacts on patients resulting from false alarms, or physical concerns like incontinence and impotence resulting from surgery for prostate cancer.

Stopping rules

There should be an independent data monitoring and safety committee. Both arms of the trial should be run in parallel until enough cause-specific deaths accumulated that would provide (say) an 80% chance of picking up a significant difference in breast cancer mortality of (say) 7%.

For this trial I propose to measure a surrogate that has good evidence to support it. Remembering the hazard rate graph shown above, the surrogate marker would be the amplitude of the peak of relapse at two years. If no peak appears in either screened or non-screened groups, then it is likely the cancer was over-diagnosed. If not, the benefit of screening might be shown in the reduction of the peak compared with control. Then we can then look at all subgroups in the same way and determine which fare best of all.

We would finally be in a position to calculate harm benefits in collaboration with consumer advocates and opportunity costs with NICE in the UK. Aids to help patients make informed decisions about their treatment options could then easily be developed as shown in this example.

(Non-clinicians in the group might be unaware that there is now a legal and ethical imperative to involve patients in decision making under such circumstances.)

Michael Baum
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Disclosure

Professor Baum is not employed in any way by a screening unit, nor does he have any financial interests within the industry.

References

1. Martin RM, Donovan JL, Turner EL, et al. Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality: The CAP Randomized Clinical Trial. *JAMA* 2018;319(9):883-895
2. Welch HG, Schwartz L, Woloshin What's making us sick is an epidemic of diagnoses. *The New York Times*, 2 January 2007
3. Gøtzsche PC, Hartling OJ, Nielsen M, et al. Breast screening: the facts – or maybe *BMJ 2009;*338:446–448
4. Baum M, Chaplain M, Anderson A, Douek M, Vaidya JS. Does breast cancer exist in a state of chaos? *Eur J Cancer* 1999;35:886–91
5. Baum M, Demicheli R, Hrushesky W, Retsky M. Does surgery unfavourably perturb the "natural history" of early breast cancer by accelerating the appearance of distant metastases? *Eur J Cancer* 2005 Mar;41(4):508-15
6. Cuzick J, Sestak I, Forbes JF, et al, on behalf of the IBIS-II investigators. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial *Lancet* 2014;383:1041–48
7. Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group, Forbes JF, Cuzick J, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol* 2008 Jan;9(1):45-53
8. Demicheli R, Retsky MW, Hrushesky WJ, Baum M. Tumor dormancy and surgery-driven interruption of dormancy in breast cancer: learning from failures. *Nat Clin Pract Oncol* 2007 Dec;4(12):699-710
9. Demicheli R, Retsky MW, Hrushesky WJ, et al. The Effects of Surgery on Tumor Growth: A Century of Investigations. *Ann Oncol* 2008;19(11):1821–8
10. Hiller JG, Perry NJ, Poulogiannis G, et al. Perioperative events influence cancer recurrence risk after surgery. *Nat Rev Clin Oncol* 2018;15(4):205–18

Appendix

From the IBIS II trial of Anastrozole for prevention of breast cancer (reference 6).

"Analyses were done on an intention-to-treat basis. A secondary per-protocol sensitivity analysis was done after some enrolled women were subsequently identified as ineligible. Initial assumptions for power calculation were based on an incidence of six cases of breast cancer per 1000 women per year, and a compliance-adjusted reduction in incidence of breast cancer of 50% with anastrozole. This calculation led to a sample size of 4000 women. However, interim figures indicated that incidence of breast cancer was higher than predicted: the overall event rate was 6·6 cases of breast cancer per 1000 women per year, which, with a 50% reduction in the anastrozole group, would translate to nine cases of breast cancer per 1000 women per year for placebo. Therefore, the sample size was reduced to 3500 women. The expected number of new cancers after a median of 5 years of follow-up for a total trial size of 3500 women was 78 in the placebo group and 39 in the anastrozole group, leading to a power in excess of 90% for a 5% significance level."(6)

BOOK REVIEW

Malignant: How Bad Policy and Bad Evidence Harm People with Cancer

Reviewed by Till Bruckner

"Malignant: How Bad Policy and Bad Evidence Harm People with Cancer" by Vinayak K Prasad. Johns Hopkins University Press: May 2020 RRP £21.49

"Ultimately, the purpose of cancer medicine is to use as few drugs as possible for as little time [as possible] to minimize side effects while simultaneously maximizing survival and quality of life," writes Vinay Prasad in *Malignant*, a book that forcefully argues that people with cancer are being let down by the way oncology is performed today.

At the outset of the book, Prasad lays out evidence that most new cancer drugs provide little or no benefit to patients. To speed up the market entry of new treatments, regulators routinely approve drugs based on clinical trials demonstrating improvements only in progression-free survival and other surrogate endpoints. However, one study found that only 14% of cancer drugs originally approved on surrogate endpoints were later proven to prolong patients' lives. Pharma companies charge sky high prices for new cancer drugs, but their true value often hovers around zero as they expose patients to harm without providing any meaningful benefits.

The next section deals with hype, spin and financial conflicts of interest in oncology. Prasad rolls out all the usual suspects, from breathless press headlines about supposed 'breakthroughs' to conflicted key opinion leaders singing the praises of pharma companies and their wares. While I'm generally unenthusiastic about efforts to conduct more research into these dynamics – adding more evidence to the existing pile seems unlikely to solve any problems – Prasad uses the occasion to raise the very uncomfortable question of whether medical opinion leaders' widespread silence on the topic of drug prices may be due to industry influence.

The book then circles back to the design and interpretation of studies of cancer treatments. Prasad takes the reader on a fascinating journey through observational data, trial designs and trial outcomes, tracing how the evidence base for various cancer treatments has shifted over time. Inevitably, this discussion can get extremely technical (unidirectional crossovers, anyone?) and the editor has allowed too many acronyms to slip through the net, but perseverance is ultimately rewarded. For example, the trial that documented a "statistically significant 10-11 day improvement in median survival," that is used to illustrate Prasad's counterintuitive argument that too large trials can be just as problematic as underpowered studies.

The final section sets recommendations for improving cancer medicine. "The metric of a successful regulatory system is not how many drugs are approved but how many drugs with meaningful benefits are approved," Prasad writes. He calls on the U.S. Food and Drug Administration to "just say no" more often when confronted with underwhelming trial designs or outcome data. The FDA "already has the regulatory authority to define the size of benefit that warrants approval," so the agency could significantly raise the evidence bar without new legislation, he notes. Longer term, Prasad proposes a system in which pivotal clinical trials are designed and run by federal agencies rather than by pharma

companies, and in which drug prices are tied to actual clinical value added.

The key strength of this book is Prasad's deep expertise on the subject matter combined with strong opinions that nevertheless steer clear of extreme positions. For example, he concedes that in some cases, temporary 'accelerated approval' based on unvalidated surrogate endpoints may be appropriate – if, but only if, regulators mandate postapproval studies and subsequently withdraw any drugs that fail to deliver on their initial promise. In addition, *Malignant*'s readability is boosted by a smooth writing style that marks a significant improvement over Prasad's first book, *Ending Medical Reversal*.

While much of the book narrates Prasad's own research, even those who follow his academic publications will find enough new material to keep them going to the end. In sum, *Malignant* is a must-read for anyone interested in evidence-based medicine, oncology or clinical trials.

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- The assessment and testing of all medical and nutritional treatments, products and procedures
- Consumer protection in regard to all forms of health care
- The highest standards of education and evidence-based health care by practitioners
- Better understanding by the public and the media of the importance of application of evidence from robust clinical trials

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