bmj.com/podcasts Marion McMurdo discusses the problem of non-representative cohorts in the *BMJ* podcast bmj.com/multimedia

Clinical research must include more older people

Why are the people who take part in clinical research so different from those seen in practice, asks **Marion McMurdo**

If recruitment to heart failure trials is a valid measure of how well the research community has progressed in embracing the participation of older people in research, then the cause may be all but lost.

Recent analysis of the World Health Organization International Clinical Trials Registry showed that of 251 trials investigating heart failure treatments, a quarter excluded patients via an upper age limit, and 43% had at least one poorly justified exclusion criterion.[1]

An analysis of a large cohort of Medicare beneficiaries with heart failure—a disease in which 80% of patients are older than 65 years—reported that only a paltry 18%, 13%, and 25% of those over 65 met the enrolment criteria for the landmark SOLVD, MERIT-HF, and RALES trials. The analysis proposed convenience and study efficiency as reasons.[2]

We have known for years that older people are systematically excluded from clinical research, with those older than 85 years particularly under-studied, a population highlighted in Age UK's *Improving Later Life—Understanding the Oldest Old*.[3] In 1992 Nanette Wenger observed that "the profile of cardiovascular illness in the United States has shifted to encompass predominantly elderly populations. Yet it is precisely in this population that the traditional exclusion, or at best under-representation, of elderly people in clinical trials has generated an information void."[4] Depressingly, few signs indicate that void being filled two decades later.

Age bias in research has been well documented in the cardiovascular literature.[5 6] Perhaps cardiovascular colleagues are particularly intransigent. Surely more enlightened researchers, such as those publishing in specialist ageing journals, can show how to undertake inclusive research? Not if a review of 434 consecutive papers in the *Journal of the American Geriatrics Society* is anything to go by.[7] The review found frequent, often unexplained, and usually unacknowledged exclusion of older people with cognitive impairment and dementia. Journals specialising in Parkinson's disease fare little better. Despite Parkinson's disease having a prevalence of 3.5% among people older than 85, almost half of all actively recruiting trials excluded participants by age, particularly smaller trials.[8]

Does it matter that research participants are systematically different from patients seen in clinical practice? Most research is still done on younger adults, often male, with single diseases and minimal comorbidity. Most healthcare users are old, multimorbid, and taking multiple drugs. This poses a dilemma for healthcare professionals when managing their frail older patients. Either they do not prescribe a treatment because of a dearth of age and morbidity relevant data, possibly depriving such people of the benefits of therapeutic advances, or they prescribe despite a lack of data and potentially expose their patients to unnecessary hazard. Both scenarios may disadvantage older people.

Clinical practice is underpinned by evidence. But evidence about caring for older people with common medical conditions remains shamefully lacking.

And what about the impact on guidelines? Clinical guidelines usually synthesise evidence on single diseases from studies carried out in narrow subsets of the population, often excluding older people and those with multimorbidity. Unfortunately, most people with a chronic condition do not have single diseases in isolation and so are likely to be the target of multiple guideline recommendations producing complex, burdensome treatment regimens with more adverse drug reactions.[9] The failure of many guidelines to consider the cumulative effect of treatment recommendations on people with multimorbidity, including older people, is increasingly recognised.[9 10]

Ethics committees should reject all proposals with arbitrary upper age limits, and journals should do likewise

Ageism in clinical research has persisted despite many creditable efforts, including championing the rights of older people to participate in clinical trials (www.predicteu.org); strong recommendations from researchers in ageing and the National Institute for Health Research to avoid arbitrary upper age limits[11]; and the publication of a guide on how to recruit more older people into studies.[12]

Most improvements in outcomes for disease treatment and management come from high quality, randomised, clinical trials. More clinical trials must embrace the heterogeneity and multimorbidity of old age in their study designs and funding. Research funders should be held to account for the equity and inclusivity of research programmes, and oblige researchers to justify eligibility criteria that are likely to be overtly or covertly ageist. Ethics committees should reject all proposals with arbitrary upper age limits, and journals should do likewise. Perhaps it is time to emulate our paediatric research colleagues, and use regulation to enforce the inclusion of older, multimorbid participants in relevant clinical trials. It is astonishing that there is no requirement that the population most likely to receive a drug once it is licensed actually participates in its evaluation.

Better management of older people is a key priority for health systems globally. The status quo of excluding older people from research is no longer supportable. This matters for our older patients today, and for all of us tomorrow.

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FROM THE FRONTLINE **Des Spence**

Saying no to chemotherapy

"Dad: eggs and salt are bad for you, teacher says." "Nonsense: you mustn't believe everything you are taught at school." There is an art to poaching eggs, and I have one with salt every day for breakfast. I ignore health scares about food, because the more health conscious people are the more miserable they become. Likewise, the benefits of screening or health check-ups make no intuitive sense to me. So, on a personal level I happily ignore the advice of "experts." Risk is about judgment, and you can be too careful. Life is for living.

But saying no to patients isn't so easy. They trust doctors: "Whatever you think, Doctor." Likewise, doctors are cuffed by guidelines, telling us to intervene even when we think we shouldn't. No doctor is criticised for doing too much; the easy thing is always to intervene. So doctors spectate on the march of medicalisation, overdiagnosis, and overtreatment. History will judge our era as one of iatrogenic harm.

Death is sad, but it must be borne and normalised. Palliative chemotherapy steals away the most precious time

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And this is a problem with cancer treatments. There have been great advances in treatments and survival (partly because of overdiagnosis of non-progressive disease). And if cancers cannot be cured then many can be contained. But there are unresponsive solid tumours and metastatic disease for which chemotherapy becomes merely palliative, and the prolongation of life is short, if it happens at all. Patients are offered ever more chemotherapy, but most are unaware that it has limited benefit.[1] This is wrong.

Chemotherapy involves frequent attendance at hospital, admission, surgical lines, and infusion or transfusion. It makes patients feel unwell—some mildly, some badly—and is occasionally fatal. Patients become ensnared in the hospital system, often dying in hospital and not at home as many would wish. Worse, it offers false hope.

Death is sad, but it must be borne and normalised. Palliative chemotherapy steals away the most precious time. So why use chemotherapy when it is worse than futile? Perhaps because there is pressure from families and patients "to do something." Perhaps the media peddle unrealistic expectations. Perhaps patients are on a depersonalised conveyor belt of intervention. Perhaps because of fear of taking away hope. Perhaps doctors are too afraid to talk about death, which we see as professional failure.

Certainly, its use is a consequence of a lack of continuity across hospital and general practice. And certainly, it is easier to offer treatment than not. We need to support dignity in death, and this often means saying no to chemotherapy. There is an art to medicine: knowing when to intervene but, more importantly, also knowing when not to.

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LAYING FOUNDATIONS **Oliver Ellis**

Suicidal memes

Richard Dawkins defined a meme as a unit of culture that causes its host, a human brain, to spread it to others, much like viruses.

In its recent issue on the topic of fiction, the US arts magazine *Vice* published an article called "Last words," with photographs of glamorous stagings of the final moments of several female authors who committed suicide.

Just as some pathogens kill their hosts while spreading, memes can too. Think of the unscientific reports that turned parents against the MMR vaccine. Think of polio ripping around Afghanistan, Nigeria, and Pakistan because of rumours about the vaccine rendering girls sterile.[1 2]

In its submission to the Leveson inquiry into UK press ethics the charity Samaritans showed how irresponsible reporting of suicide can increase suicide rates.[3] The charity provides guidance to UK media on responsible reporting of suicide. But the internet is international, and most of the harmful material is posted and replicated not by media organisations but by individuals.

And so the "Last words" meme went viral. The *Guardian* picked it up. Worryingly, the online version I saw ended with: "This article was amended on 18 June 2013 to remove a reference to a particular method of suicide."[4] *Vice* removed the article from its website.[5] But the images are still available on the internet, mostly right next to criticism of *Vice* for publishing them.

And here I am now, spilling yet more ink over it. The meme is in my brain, and in these pages. You might not have heard about this controversy before; or you might have forgotten about it. But now it's in your brain too. So why bring it up again? Because memetics is a public health issue. The availability of the internet makes it even more dangerous. Society must take action.

If a restaurant put its customers at risk of food poisoning, it would be shut down. Society feels quite comfortable risking restaurateurs' livelihoods for this. So why are we uncomfortable about restricting speech to prevent harm on a much larger scale? The internet is a modern day, public water well that nobody should be allowed to poison with harmful material.

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We cannot have a society where the public is excluded from debate on topics such as vaccination. But the debate needs to be informed and scientifically rigorous. Free speech is a right. But as with all rights it isn't absolute. You can't shout "Fire!" in a theatre. You can't reveal the nuclear launch codes. You can't publish a recipe for making a weapon from anthrax. Why? Because these things will cause misery, death, and destruction.

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