

Clinical Trials: An Overview

A talk prepared for an INSPIRE workshop on research, for medical students in York.

J Martin Bland

Emeritus Professor of Health Statistics
University of York

What is a clinical trial?

A clinical trial is a study where a potential treatment for a health problem is tested. This is usually on the sick, but not always. We also have vaccine trials, for example. The participants may be human or animal, but the sick animal is naturally sick, e.g. veterinary trials. These are different from laboratory experiments, where ill health may be induced in an animal. I would not describe those studies as clinical trials. In a clinical trial, the welfare of the research participant, of whatever species, is our primary concern. In this talk, we shall be concerned only with human medicine.

How clinical trials work

A clinical trial is a complicated type of study. The topics which I shall discuss in this talk include:

- ❖ phases
- ❖ research team
- ❖ acronyms
- ❖ funders
- ❖ trial teams
- ❖ getting permission
- ❖ recruitment
- ❖ analysis
- ❖ reporting

Phases

Trial research is usually grouped into three phases, Phases I, II, and III.

Phase I: First steps

Phase I trials, as we might expect, are the early tests of the treatment on humans. These include “first in human” studies, where the treatment is tried on healthy volunteers. In drug development these are usually male and so described as “first in man”. We would use women only if this is essential. This is to avoid any risk of affecting an unborn child. Sometimes, this is not possible. For example, in the trial “MABGEL” we tested a vaginal gel, designed to prevent HIV transmission. The gel contained three mono-clonal antibodies. We were concerned with the persistence of the gel in the vaginal secretions and in transfer of the antibodies to the bloodstream. All women had to be using effective contraception.

Another feature of Phase I trials is dose finding, where we look at the effects of different levels of our treatment to discover what might be worth studying further, bearing in mind the

need for both efficacy and safety. In MABGEL we compared two levels of antibodies and the vehicle only.

Pharmacokinetics is a third aspect of Phase I trials, where we look at how a drug is metabolised in the human body. In MABGEL, we estimated the half-life for each antibody in different locations.

Phase 2: Efficacy

Phase II trials are small to moderately sized comparative trials. They address issues of efficacy and feasibility: whether this treatment appears to work in the disease group of interest, whether we can we apply it in normal clinical practice, etc. These include proof of concept trials, where we aim to show that there is good evidence that the treatment has the required activity. For example, the AVURT trial of aspirin for the treatment of venous leg ulcers seeks to determine whether the evidence from a small and rather inefficiently designed trial of this treatment can be repeated on a larger scale. Most cross-over trials, where participants receive more than one treatment in succession, are Phase II trials, because there cannot be any long term follow-up of participants and because they typically have small sample sizes. An example of a planned but as yet unfunded Phase II cross-over trial is of automated monitoring of glucose for insulin-using people with diabetes who have impaired glycaemic awareness. The meter reports the glucose measurements to a central office, where they are analysed and if the person appears close to a hypoglycaemic state they are send a warning and advice to take glucose quickly. Participants would have the warnings switched on for one period of the trial and switched off for another period.

Phase 3: Effectiveness

Phase III trials are much larger comparative trials, where the new treatment is compared to the currently accepted treatment. They are often multicentre or multinational trials, because a single centre does not have enough potential participants. An example was ICSS, the International Carotid Stenting Study, where we compared the relieving of constrictions of the carotid artery, with the attendant risk of stroke, by angioplasty and insertion of a stent with surgical vein grafting. This trial included participants from 50 academic centres in Europe, Australia, New Zealand, and Canada. Phase III trials are of treatments which are thought to be almost ready to implement in routine practice. They usually have economic analyses to help decide whether the new treatment would be cost effective, i.e. whether the health gain would be worth the resources required.

Cluster randomised trials, where all potential participants in some geographical location or service unit are allocated to the same treatment, are almost always Phase III trials. An example was CADET, a trial of the management of depression diagnosed in primary care. General practices were allocated to collaborative care, where a mental health worker shared the care of depressed patients with the GP, or to treatment as usual.

Research team

It is very difficult to do clinical trial research alone; we need a team which includes people with multiple skills. For example, we may need researchers from more than one clinical specialty. For example, UKTAVI, a trial comparing insertion of replacement heart valves by angioplasty with surgical insertion, required a team including radiologists, cardiologists, and cardiac surgeons. Apart from clinical personal (medical, nursing, etc.), we may need people who are expert in statistics, economics, psychology, sociology, etc., depending on the condition and the intervention.

To enable access to these skills by clinical researchers, clinical trials units have been set up based in several universities and also commercially for the pharmaceutical industry. These offer support with study design, random allocation including remote 24 hour randomisation services, form design, data collection, analysis, etc. A shining example is the York Trials Unit, based in the Dept. of Health Sciences, University of York.

Acronyms

Every trial needs a name. This is essential, because they involve so many people and go on for years. Many researchers are working on several at the same time, in trials units, for example. The descriptive name of the trial is usually long and intricate, so the custom is to use an acronym derived from this. These are sometimes rather tortured. Here are some examples:

- ❖ UKTAVI: **U**nited **K**ingdom **T**rascatheter **A**ortic **V**alve **I**nsertion **T**rial.
- ❖ MABGEL: A randomised double blind phase 1 study to assess the pharmacokinetics of C2F5, C2G12 & C4E10 when administered together in a gel vehicle as a vaginal microbicide. (**M**onoclonal **a**ntibodies in a **g**el vehicle.)
- ❖ CADET: Multi-centre Randomised Controlled Trial of Collaborative Care for Depression (**C**ollaborative **C**are for **D**epression **T**rial)
- ❖ VenUS: **V**enous Leg Ulcer Study (+ II, III, IV)

Funding

Clinical trials are often very expensive to set up and run, costing millions of pounds in Phase III. Researchers usually have to obtain funding to run their trial. There are three main sources of funding:

- ❖ Public funds, paid for from taxation. Funders include the National Institute for Health Research (NIHR), Medical Research Council (MRC), the Scottish Office, the EU, etc.
- ❖ Charities, paid for by donations, legacies, flag days, etc. There many of these, including the British Heart Foundation, Cancer Research UK, the Wellcome Trust, the Stroke Association, etc.
- ❖ Commercial funds. Trials are funded by pharmaceutical companies, medical device manufacturers, etc.

Trials may be funded by a combination of several of these. For example, an NIHR trial which uses a licenced drug in a new way may have the drug provided free by the manufacturers, an international public-sector trial may have the sites in different countries funded by different charities or state providers in the different countries.

Trial teams

A clinical trial can be a complex enterprise and need several different groups of people to meet. These include:

- ❖ The **Trial Management Team**, which runs the trial from day to day. This usually has the principal investigator (PI), who was the lead applicant, the trial coordinator, who is paid to run the trial from day to day, a trial statistician, an economist, some of the main collaborators, trials unit staff, etc. They will meet quite often, monthly is typical.
- ❖ The **Trial Steering Committee**, which represents the funders. The members are appointed by the funders, including an independent chairperson, independent

clinicians, statistician, and economist, patient representatives, plus the PI, and some members of management team. It might meet half-yearly or yearly.

- ❖ The **Data Monitoring and Ethics Committee (DMEC)**, which represents the participants. Usually, this consists of two independent clinicians and an independent statistician. It is totally independent of the trial management and reports to the chair of the trial steering committee. The DMEC are the only people to see unblinded data during the trial. They are there to check that the trial is not harming participants. They usually meet a week or two before the steering committee.
- ❖ **Other trial workers**, who include research nurses, recruiting clinicians, computing staff, etc. These are overseen by the trial management committee. They are usually employed on the research grant or by NHS or by pharmaceutical companies.
- ❖ The **Trial Sponsor** is legally responsible for the trial. This may be an NHS trust, a pharmaceutical company, or a university. These are the people to sue if anything goes wrong and people are harmed.

Getting permission

The procedure for getting permission to run a clinical trial varies from country to country. In the NHS, we must get two or three permissions, which may take many months. We must get approval from:

- ❖ **Research Ethics Committees**, which protect trial participants. There are local committees in each area for trials to be done in that area and a system of regional committees for multi-centre studies. These include health professionals, other scientists such as statisticians, and members of the public.
- ❖ **Research Governance Committees**, which protect the health service. These ensure that the trial will be feasible within the resources of the NHS.
- ❖ The **Medicines and Healthcare Products Regulatory Agency (MHRA)**, which is a national body whose approval is needed for pharmaceutical and similar trials.

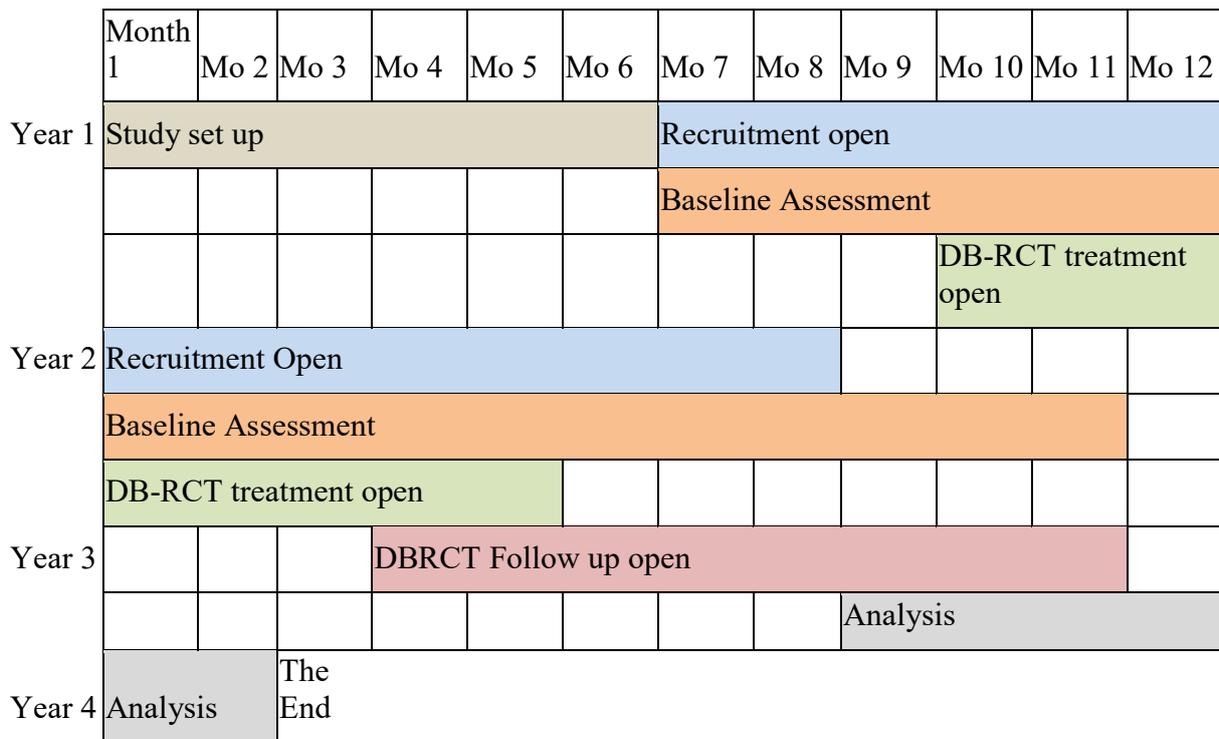
Documents

There are three key documents which we must have ready before the trial begins and which must be seen by funders and by ethics and research governance committees:

- ❖ The **Trial Protocol**, which gives detailed instructions for how the trial is to be carried out, include what the interventions are, who is to be recruited, what information is to be collected, etc.
- ❖ The **Patient Information Sheet**, or **Participant Information Sheet**, which is given to people approached to take part in the trial. This explains in simple terms what the trial is about, what will happen to participants, and what the risks are.
- ❖ The **Patient Consent Form**, which must be signed by participants and kept by the trial office.

The protocol often features a Gantt chart, which shows what we plan to happen over the course of the trial. A Gantt chart, devised by Henry Gantt about 100 years ago, looks like this the mock-up shown in Figure 1.

Gantt charts are often rather optimistic.



Total = 34 months

Figure 1. A Gantt chart

Recruitment

Once our plans are made, all our documents drawn up, funding obtained, permissions granted, collaborators and staff recruited, it is time to begin. We can start to recruit trial participants. These should give informed consent, if at all possible. They should know that they are being invited to join the trial and what it will involve, then have time to consider this and to discuss it with their families, if possible. There may be several difficulties in this.

Treatment may have to start right away, potential participants may be unconscious or they may be incompetent to consent, e.g. babies, people with dementia. As an example, Figure 2 shows the procedure from the trial TICH-2 (Tranexamic acid for Intra-Cerebral Haemorrhage). People brought into Accident and Emergency with suspected stroke will not have time to think about the trial and they may be unable to give consent due to the stroke.

For participants recruited without written consent, this should be obtained later, after things have calmed down a bit. If someone recruited in this way refuses later, we drop them from the trial and their data are not used in the analysis. Of course, as in TICH-2, it may be too late to refuse treatment once it has been given.

Children and elderly people with dementia are recruited to trials only when the treatment is specifically for them and cannot be tested on competent adults.

Participants in clinical trials are often recruited by busy clinicians: doctors, nurses, etc. This can lead to eligible people not being recruited. The clinicians are too busy to explain the trial, or simply forget. As a result, recruitment often lags behind our target. Management and steering committees all too often find themselves contemplating a graph like Figure 3, which shows the planned and the actual recruitment.

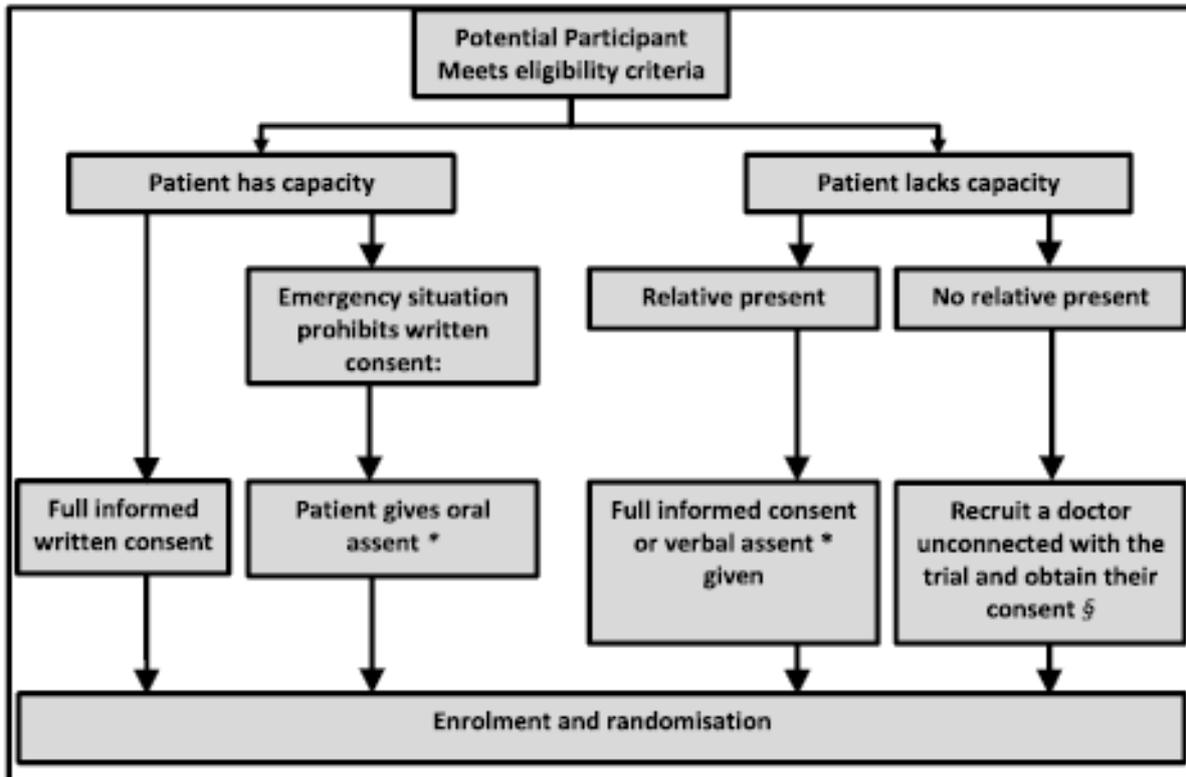


Figure 2. Procedure for recruitment and consent in TICH-2

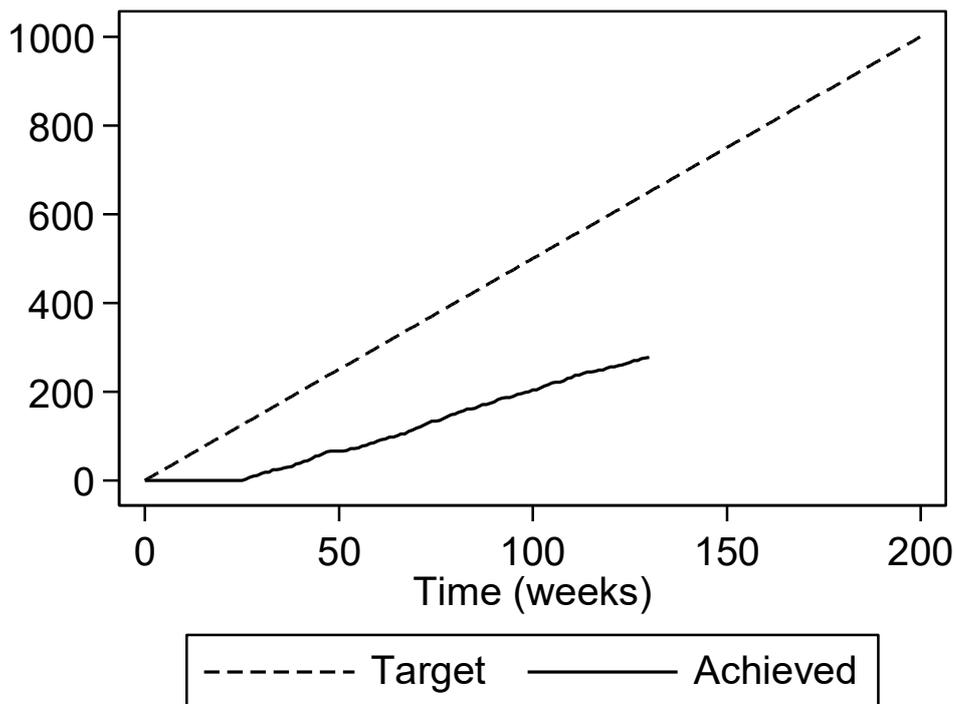


Figure 3. Typical trial recruitment graph

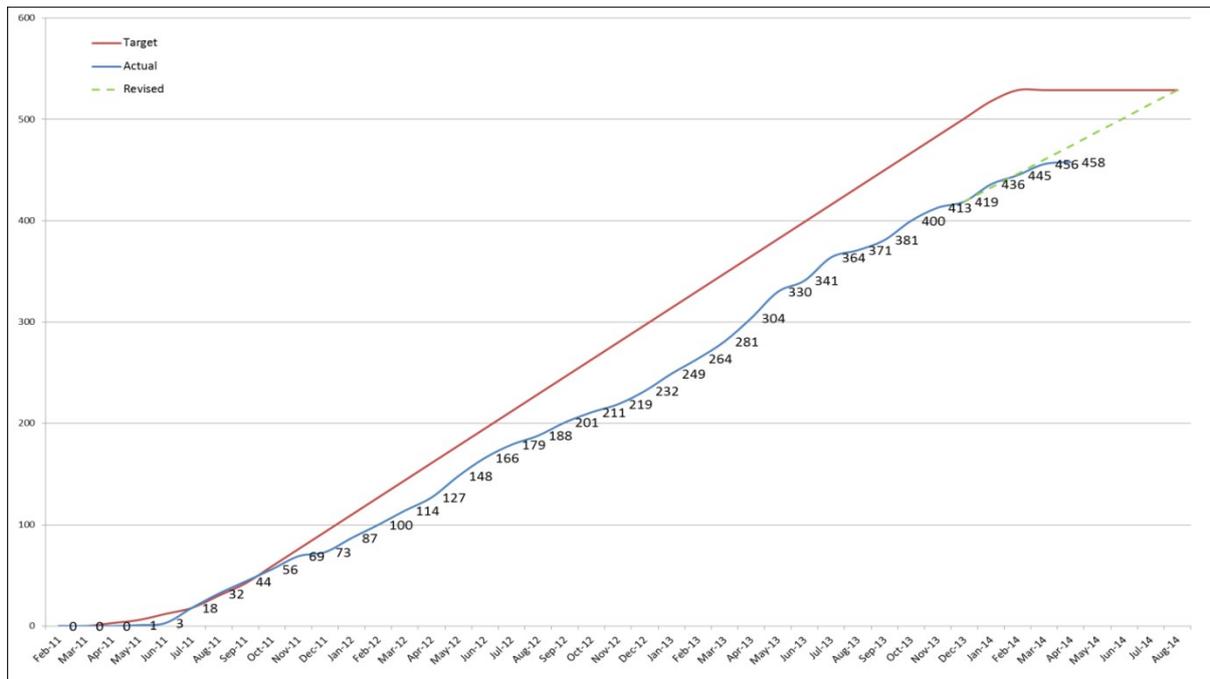


Figure 4. Recruitment graph from the HEELS trial (Evaluation of fibreglass heel casts in the management of ulcers of the heel in diabetes).

In the illustration in Figure 3, the trial has started later than planned, shown by the horizontal line for “Achieved” at the beginning. It then recruited more slowly than expected.

Sometimes we need to extend recruitment in time because of this, sometimes we need to apply for more money to maintain the employment of trials staff. When I was on the Health Technology Assessment Evaluation and Trials Board, about half of all our trials had to seek an extension in time, and some of these an extension in funding, too. Figure 3 shows this happening in a real trial, for which I was on the DMEC. This trial did recruit the full number after an extension in time.

Sometimes researchers have to abandon the trial altogether. For example, CANPOP (CANnabis for Peri-Operative Pain), for which I chaired the DMEC, could not recruit enough participants for the pre-randomisation dose ranging study. The trial itself never began. I was statistician on a trial of sublingual nitrates in acute myocardial infarction. The death rate was much lower than anticipated. The PI discovered that only the least ill patients brought in to A&E were being recruited. The registrars were giving all the rest nitrates, which they had decided was an effective treatment. We could not carry out the trial and closed it.

In research you are doing something nobody has ever done before. Unforeseen things can go wrong and they do.

Analysis

There are problems in the analysis of trials, because selective reporting can distort the results greatly. If we measure 10 different outcome variables, which is easily done, then, even if the treatments are identical in their effects, the chance of at least one outcome having a significant difference is much greater than 0.05. Trialists care deeply about their treatments and want them to succeed. They may report this outcome and play down the others.

Because of this, we should make an analysis plan and this should be agreed before recruitment has finished and we look at the data. There are great dangers in multiple testing.

We need to choose a primary outcome variable, on which our interpretation of the effectiveness of our treatment stands or falls, and we need to stick to it. The MHRA insists on the analysis plan being approved, in advance of any analysis, by an independent statistician at another institution from the trial statistician.

Reporting

And finally, the trial is complete and we can tell the world. We might hope for a paper in the *Lancet*:

Clinical and cost-effectiveness of compression hosiery versus compression bandages in treatment of venous leg ulcers (Venous leg Ulcer Study IV, VenUS IV): a randomised controlled trial



Rebecca L Ashby, Rhian Gabe, Shehzad Ali, Una Adderley, J Martin Bland, Nicky A Cullum, Jo C Dumville, Cynthia P Iglesias, Arthur R Kang'ombe, Marta O Soares, Nikki C Stubbs, David J Torgerson

Summary

Background Drawbacks exist with the standard treatment (four-layer compression bandages) for venous leg ulcers. We have therefore compared the clinical effectiveness and cost-effectiveness of two-layer compression hosiery with the four-layer bandage for the treatment of such ulcers.

Methods We undertook this pragmatic, open, randomised controlled trial with two parallel groups in 34 centres in England and Northern Ireland. The centres were community nurse teams or services, family doctor practices, leg ulcer clinics, tissue viability clinics or services, and wound clinics. Participants were aged 18 years or older with a

Lancet 2014; 383: 871-79

Published Online
December 6, 2013
[http://dx.doi.org/10.1016/S0140-6736\(13\)62368-5](http://dx.doi.org/10.1016/S0140-6736(13)62368-5)

See [Comment](#) page 850

Department of Health Sciences
(R L Ashby PhD, R Gabe PhD)

or a paper in the *BMJ*:

BMJ 2013;347:f4913 doi: 10.1136/bmj.f4913 (Published 19 August 2013)

Page 1 of 10

RESEARCH

Clinical effectiveness of collaborative care for depression in UK primary care (CADET): cluster randomised controlled trial

OPEN ACCESS

David A Richards *professor*¹, Jacqueline J Hill *PhD student*², Linda Gask *professor*³, Karina Lovell *professor*⁴, Carolyn Chew-Graham *professor*⁵, Peter Bower *professor*⁶, John Cape *head of psychology*⁷, Stephen Pilling *professor*⁷, Ricardo Araya *professor*⁸, David Kessler *consultant senior lecturer*⁸, J Martin Bland *professor*⁹, Colin Green *professor*¹⁰, Simon Gilbody *professor*¹¹, Glyn Lewis *professor*¹², Chris Manning *public and patient advocate*¹³, Adwoa Hughes-Morley *research fellow*³, Michael Barkham *professor*¹⁴

¹Institute of Health Research, University of Exeter Medical School, Exeter EX1 2LU, UK; ²School of Psychology, University of Exeter, Exeter, UK;

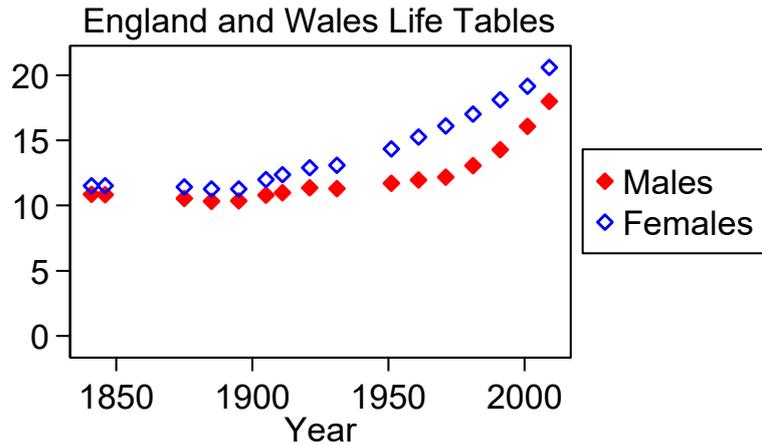


Figure 4. Life expectancy at age 65 in England and Wales since it was first estimated in 1841

Now we need to publicise our findings to people who might put the research into practice. Publication is one part of this, but another is personal contact, speaking at meetings, etc. This is a job for the clinical members of the team. It is very important. It can take a long time for research to get into practice.

Is it worth the effort?

YES!!! Since the first randomised clinical trial was published in 1948, life expectancy has improved dramatically. Figure 4 shows life expectancy at age 65, the average number of further years which a person aged 65 would live if the death rates now continued throughout their future lifespan. This is thus an indicator of death rates at all ages greater than 65.

I chose this as my measure of the effectiveness of medicine, because the 65+ age group are the main consumers of medical care. Life expectancy has been calculated for census years, which is why there is a gap at 1941. Even statisticians had other things on their minds. As we can see, there is little change over the 19th century, then at the start of the 20th century, it starts to rise slowly for women, not so much for men. One theory is that the fall in birth rate produced by the fall in infant mortality meant that women were arriving at age 65 with fewer pregnancies in their history and were thus fitter and healthier. The lines diverged until 1981, when men’s life expectancy began to improve dramatically. It then rose more rapidly than for women, so that they have almost reached parity again. I think that women outliving men was a 20th century phenomenon.

I think we can ascribe this to improved medicine and public health, which are the result of improved medical research. That is only an opinion, of course.

This presentation was originally prepared with Dr. Fabiola Martin.