How are RCTs developed and conducted in the NHS?

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Why me?

I may not be the best person to give this talk, as I have never worked in the NHS. However, I am currently on the Health Technology Assessment programme Clinical Trials Board, and have been in the past a member of an MRC project board, an NHS special funding committee, and a multicentre research ethics committee. I have also been the statistician on many trials carried out in the NHS.

Start with a question

A research project starts with a question. What do we want to know? Research questions come from two places:

- the researcher,
- the research funder.

The researcher is usually a clinician in the NHS, a university, or a research council centre. Sometimes it may be a non-clinical academic.

For example, consider the proposed randomised controlled trial VenUS IV (Venous Ulcer Study IV). This is to be a randomised controlled trial of high compression hosiery versus high compression bandaging in the treatment of venous leg ulcers. The question is: what is the clinical and cost effectiveness of using high compression hosiery compared with high compression multi-layer bandaging in the treatment of venous leg ulcers? The proposal is led by Dr. Jo Dumville, non-clinical co-ordinator of the VenUS II trial, who has undertaken research projects relating to wound care and the conduct of randomised controlled trials. VenUS IV follows the VenUS I trial of high compression bandaging, which is now the recommended treatment in the NHS. A different technology, high compression hosiery, has practical advantages to nurses and patients. Nurses want to know whether it is as effective as high compression bandaging. As an academic working closely with nurses in the VenUS II trial, Dr. Dumville responded to this need for a study by proposing VenUS IV.

The researcher can be a lone researcher or may gather a team. A lone researcher may later seek help, e.g. statistical. When I worked in a medical school attached to a hospital, I frequently had clinical researchers put their heads round my door asking whether I had five minutes. (I usually did but it usually needed much longer, so I always made them wait.) Lone researchers tend to carry out small trials, often of poor quality.

Clinical trials are a complicated affair and very few of us have all the skills necessary to develop and run one. I certainly don't. To complement their own knowledge and skills, the researcher may gather a team to develop the research proposal. Such a team might include any of the following:

- clinicians, from the same or other specialties: doctors, nurses physiotherapists, etc., may include clinicians from other potential research centres.
- professional researchers: clinical trials unit, trialists, statisticians, health economists, etc.
- other relevant professions: psychologist, bioengineer, biochemist, etc.

The VenUS IV team includes:

- clinicians: professor of nursing,
- professional researchers: director of York Trials Unit, statistician, health economist,
- other relevant professions: none.

Funding

Having got our team together, we now move the next step. Can we do the trial from existing resources or do we need external funding? Most clinical trials are expensive. They require staff to be employed and treatment to be paid for. We might get this from:

- local NHS, university, or research council pump-priming funds,
- Medical Research Council,
- Health Technology Authority (e.g. this was where we went for funding for VenUS IV),
- other NHS funds,
- charities, e.g. Welcome, Cancer Research UK, British Heart Foundation,
- industry, such as the manufacturers of drugs or devices to be evaluated in the trial.

More information about this is given elsewhere in the Master Class programme, so I won't go into any more detail now. Funding is usually two stage process:

1. outline proposal,
2. full proposal.

We start with an outline proposal. This is usually a short descriptions of:

- the question,
- the background,
- the research design,
- the research team,
- estimate of cost.

At the meeting of the funding board, three or four designated board members will speak about the outline, having prepared written comments. It is worth remembering that the board members may have thirty such proposals to consider and be asked to comment in detail on five of them. (It can be much worse; for one funding board I was asked to provide written comments on 50 of the 150 proposals received.) Not all of the board members will be able to read all proposals in detail and applicants must be clear. Don't try to pack in as much information as possible in a dense mass of type. Board members then discuss the proposal and agree whether to invite a full proposal. Many proposals are rejected at the outline stage. Half would be typical.

The funding board may make suggestions for (what they see as) improvements to the proposal. Negotiation between funders and applicants may result in changes to the proposal, including additions to the team. It is worth noting that funders are asked to look for value for money and do not like padded proposals. Asking for £10,000 for a PC and printer will not go down well. On the other hand, if a proposal looks far too cheap to be feasible, funders will actually suggest that applicants look again at whether they need more money. I have seen this happen, really!

For successful outline applications we can then proceed to a full proposal. The full proposal is much more detailed and much longer. It includes financial details, both costing of each aspect of the research and of the treatment. Applicants need to apportion costs between research (to be paid by the research funders) and treatment (to be paid by the NHS). Full proposals are sent to referees from the clinical area being researched and to trial methodologists. Typically six referees might be asked to comment on a proposal. Applicants may have the opportunity to reply to referees' questions and/or comments before the board meeting.

At the meeting of the funding board, three or four designated board members will speak about the proposal, the referees' comments, financial arrangements, etc., having prepared written reports in advance, as before. Board members then discuss the proposal and score it. High scoring proposals are funded. About half of applications are rejected as the full proposal stage. Negotiation between funders and applicants may result in further changes to the proposals which are going to be funded. Amended proposals may have to come back to the board for a further discussion, but most are agreed by email between the designated board members, chair, and secretariat.

By now a year has passed!

An alternative route to funding

An alternative route to funding is research commissioned by the funding body. Funders might see the need for an answer to a specific question, such as whether a new technology being advertised to the NHS would be cost effective if introduced widely. For such a question, the funder will put out a specific tender. Applicants interested in carrying out this research can then bid for this commission by putting in proposals.

For example, recently the HTA put out to tender a feasibility study and trial protocol development for a UK based screening programme for lung cancer utilising low dose computerised tomography. This had a fairly detailed brief:

1. Technology: Low-Dose Spiral Computerised Tomography (CT) scanning.
2. Patient group: Researchers should identify and justify the selection of a suitable target population in the UK.
3. Setting: A UK population based screening programme.
4. Design: The design is to be a controlled trial. The protocol for the trial should be powered at the level of 90% or greater.
5. Comparator: Unscreened population receiving standard care.
6. Primary outcome Lung cancer mortality rate.
7. Secondary Outcomes (informed by NSC criteria): The diagnostic accuracy of spiral CT in a screening population (sensitivity and specificity), lung cancer detection rates, harms within a UK secondary care setting, psychological impact, quality of life, screening uptake and acceptability, pre & post screening smoking status and estimates of the cost-effectiveness and cost utility of screening.
8. Intermediate results: A report is required at the end of the pilot study to help the HTA programme come to a timely decision about the viability of proceeding to the full trial. This should include any proposals for varying parameters or other aspects of the trial and if appropriate, revisions to the proposed costs.
9. Duration of follow up. The duration of the pilot study and the full trial should be justified in the proposal.

For calls like this an *ad hoc* board might be set up, made up of some current board members (e.g. myself) and possibly outside specialists in the field. Proposals are required to address this brief and the board then considers proposals received and chooses one to commission, if possible. The usual process of change and negotiation may also take place at this stage.

Rather than a specific question, funders may put out a special call looking for proposals related to a particular topic. For example, the HTA recently put out a themed call for proposals for health technology assessment research in the area of Healthcare Associated Infection. The brief specified only that:

> "This call will consider research relating to healthcare associated infections associated with hospitals or occurring in the community, for example in primary care, in nursing homes or in community care. This call includes research on prevention, diagnosis and treatment and is not limited to specific patient groups or types of infection."

Researchers whose question fits this area apply and then the process is as for spontaneous applications.

The next steps

Once the study is funded, we must now obtain:

1. research ethics approval
2. research governance approval

The research ethics committee:

- is there to protect the patient from exploitation,
- will also check the scientific validity — poor research is unethical,
- usually will not consider studies waiting for a funding decision — too many design changes take place during the funding process.

The NHS research governance process:

- is there to protect the NHS,
- gives management approval for research studies involving the use of any NHS resources (staff, facilities, NHS patients, patient data, patient samples or tissue),
- will also check the scientific validity of the proposal if this has not been done elsewhere.

We now set up some committees of our own, to oversee the research. These are usually:

- Trial Management Committee, which carries out day to day oversight of the trial, meets every few weeks, and consists of the applicants and staff employed on the project,
- Trial Steering Committee, which represents the trial to funders and other bodies such as the research ethics committee, meets once or twice a year, and has outside members in addition to the applicants, usually with an outside chair and often with a patient representative,
- Data Monitoring and Ethics Committee, a small group which monitors the data as the trial proceeds, may recommend stopping the trial if participants are being harmed, and is also very useful if things go wrong and more money is needed, as it can give a confidential view on the likely outcome of the trial to the funding body.

And finally . . .

Now do the research!