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Why do clinical trials in general practice?

Ultimately what we do as doctors is intervene in our patients to alleviate symptoms (palliate), or reduce risk (prevent), or abort (cure) disease processes. Such interventions do not have to be drugs. They can be simple prognostic reassurance, an exercise regimen, counselling, meditation, or any other modality of care.

If we are to utilise such interventions we need to know that they work, ie. have efficacy and that they do not have a large burden of adverse effects, ie. are safe. Interventions should never be assumed to be benign. There are adverse effects for all interventions, which can be minor or profound (eg. if you recommend that someone gets regular exercise they can invert an ankle or be struck by a truck while cycling).

Clinical trials are traditionally conducted in secondary or tertiary care. So why do we need to do them in general practice? A nonexhaustive list includes:

- Many trials need large numbers of participants due to the rarity of important endpoints (eg. the onset of dementia). Our strong interaction with the community means we are well placed to identify eligible participants
- The prevention paradox – whereas the highest risk individuals are secondary prevention population, the greatest number of at risk individuals are in the primary prevention population. This means that, from a population perspective, primary care is where the most can be done
- The different burden of disease. Minor common conditions are usually not treated in secondary care. If we don't do this research who will?
- Access for conditions that are transient or may have a limited window of therapeutic opportunity. For example, the age old debate of the benefit of steroids early in the presentation of Bell palsy was finally answered through ready access of community sufferers early in their disease to a Scottish primary care research network[1]
- Effectiveness versus efficacy. General practice trials demonstrate what works in the real world as opposed to the controlled environment of a clinical trials centre. We are at the blunt end of research rather than the pointy end of 'new breakthroughs'. Very few 'breakthroughs' make it into clinical practice. Translational research is needed by earlier research groups to get these innovations into practice. (Witness the languishing of pharmocogenomics in primary care due to the failure to conduct such research)
- Generalisability. Restrictive inclusion/exclusion criteria often makes it difficult to relate the participants in a trial to the complex unscreened patient sitting opposite the general practitioner in the consulting room. Trials in general practice are on 'real' patients. It can be said that research can only be directly applied to the population it was conducted in.

ASPREE as exemplar

ASPREE (ASPirin Reducing Events in the Elderly), a large, randomised, double blind, placebo controlled trial of low dose aspirin in people aged 70 years and over is an international standard clinical trial in general practice in Australia. From the outset it has been designed to answer a question relevant to GPs and their patients.

US Preventive Services Task Force guidelines reasonably assume that the use of aspirin for the primary prevention of cardiovascular disease should be based on absolute cardiovascular risk score.[2] However, few of the participants in the primary prevention trials of aspirin were elderly and a meta-analysis of these trials failed to prove benefit over harm. It is also assumed in a drug trial that the adverse event rate is relatively static across the study population. This cannot be assumed in the aged population. For example, the risk of major gastrointestinal bleeding in those over the age of 50 years rises exponentially with age.[3]

As our patients age, Ockham's razor breaks down. Our elderly patients suffer from multiple disease processes and a reduced physiological capacity to cope with them, and the interventions we ply them with. It seems reasonable therefore, to expand the outcomes investigated in ASPREE to capture these possible harms and benefits, such as reducing other prevalent diseases in the aged (eg. colon cancer and dementia). This is captured in the ASPREE primary endpoint which is the prolongation of a healthy active life (free of dementia and disability) rather than just a single disease outcome such as stroke or heart attack.

Approximately 1500 GPs and 12 500 patients will participate in ASPREE. Major funding bodies of the ASPREE trial are the National Institutes of Health (USA) and the National Health and Medical Research Council of Australia. Bayer Healthcare is providing in-kind support through the provision of trial medication. For a full description of the trial methods or how you can participate in ASPREE, please refer to the ASPREE website at www.aspree.org or www.med.monash.edu.au/epidemiology/cardiores/aspree.html.

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