

The causes and effects of socio-demographic exclusions from clinical trials

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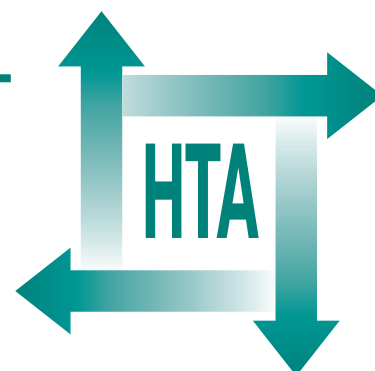
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Executive summary

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Executive summary

Background

The exclusion from trials of people likely to be in need of or to benefit from an intervention could compromise the trials' generalisability. We investigated the exclusion of women, older people and minority ethnic groups, focusing on two drug exemplars, statins and non-steroidal anti-inflammatory drugs (NSAIDs).

Objectives

- Scope the social, legal and ethical contexts of trial exclusion, comparing the UK with the USA.
- Document disparities between people included in trials, those using the drugs and those in need of the treatment.
- Project the effects of exclusion on the generalisability of trials, referring to effectiveness (statins) and adverse effects (NSAIDs).
- Develop a theoretical model for the causes and effects of exclusions.

Methods

Scoping

We reviewed literature on the exclusion of women, older people and ethnic minorities in healthcare research and held three workshops with stakeholders.

Trials

We analysed 27 randomised controlled trials (RCTs) of statins use for secondary prevention of coronary heart disease (CHD), lasting at least 6 months (up to August 2001). We analysed a stratified sample of 25 NSAIDs trials for pain in osteoarthritis (OA) (up to 1998, prior to the introduction of coxibs).

Cohorts

Using a Scottish cohort with record-linkage [Medicines Monitoring Unit (Dundee) (MEMO)], we profiled 3188 people needing secondary prevention for CHD (1993–1996), ascertaining the independent effects of statins, and 131,410 people dispensed NSAIDs (1989–1996), examining adverse effects.

Use and need

To profile the need for secondary prevention of CHD in England we accessed routine data sources including Hospital Episode Statistics (HES). To estimate usage we consulted published surveys. For potential need and usage of NSAIDs in OA we accessed the Somerset and Avon Survey of Health (SASH) 1996–97 and published data.

Disparities

For both drugs, we compared the socio-demographic profiles of trial samples, the population in potential need and those on treatment.

Epidemiological/statistical assumptions

We produced an evidence synthesis to clarify the effects of statins on women and older people. We modelled the relationship of absolute effectiveness outcomes (e.g. numbers needed to treat) with underlying risk levels of disease events, examining the likely effects of trial exclusions.

Results

Scoping

In the USA, the discourse has expanded from protecting the vulnerable to include justice and the equitable access of different groups to trials. Appropriate representation of women and ethnic minorities in publicly funded trials is required by legislation. Guidelines recommend appropriate inclusion by age. In the UK, the debate is more limited, and equity and inclusivity in research are not formally promoted.

Trials

Statins

The average age of trial participants was 58.5 years; only 16.3% were women. Statins reduced cardiovascular disease (CVD) incidence by about 25% in both men and women. Older people up to 75 years of age also benefited. Meta-analysis and two landmark trials, containing large proportions of women and older people (published after 2001), confirmed these results.

NSAIDs

The average age of trial participants was 61.9 years and women were well represented

(68.5%). Gastrointestinal (GI) adverse events were commonly reported, but renal side-effects were not. Outcomes were seldom reported according to socio-demographic group.

For both drugs, USA trials were more inclusive than UK/European trials. Ethnicity was not well reported for either drug.

Cohorts

Statins

Some 23% of the cohort were treated with statins. Statins users were younger than non-statins users (but no more likely to be male) and had superior outcomes.

NSAIDs

High current exposure to NSAIDs elevated the risk of GI side-effects by about 50% versus no current exposure and renal impairment risk by nearly 140%. Side-effect risk increased with age; being female diminished risk.

Use and need

Statins

Approximately 537,000 incident cases of CVD would qualify for statins use in England each year. Women constitute 45% of this population with need, two-thirds of whom are aged 65 years or over. Need varies by ethnic group. No sex bias in prescribing was detected, but use was commoner in younger people.

NSAIDs

6.3% of adults aged 35+ years reported hip and/or knee pain associated with OA; 3.9% of adults used prescribed analgesics for this and they were more likely to be women and to be >65 years old.

Disparities

Statins

Women formed almost half of the 'with need' and 'on treatment' populations, but were markedly under-represented in trials. Those aged 65+ years formed nearly two-thirds of the 'with need' population, but only one-fifth of trial samples, and were less likely to be treated than younger subjects.

NSAIDs

Women formed similar proportions (two-thirds) of trial samples, and of the 'with need' and 'on treatment' populations. People aged 65+ years formed about three-fifths of the 'on treatment' population, but were under-represented in trials. Association of side-effects with socio-demographic factors was revealed in cohort data but not in trials.

Epidemiological/statistical assumptions

Meta-analysis might overcome problems of low inclusion for the assessment of relative effectiveness, but the assessment of side-effects in different groups would require massive trials. Measures of absolute effectiveness are vital for the analyses of benefit and harm and cost-effectiveness. Such measurements, involving underlying risk levels, will be severely biased if different population groups are not adequately represented.

Main conclusions

The issue of exclusion from trials of women, older people and ethnic minorities has been relatively neglected in the UK research community, and there is confusion about diversity issues. Under-representation occurs, but in drug trials at least this may not always affect the external validity of relative effect estimates. However, measures of absolute effectiveness, absolute harm and cost-effectiveness are associated with underlying risk levels in different socio-demographic groups. Under-representation will therefore bias absolute effect estimates. The complexity of the issues made development of a theoretical model impossible.

Recommendations for future research

The following areas are suggested for future research:

- Multi-disciplinary assessment of realistic options for trialists to address the issue of exclusions.
- Clarification of the use of ethnic categories in health research and of the implications of the different dimensions of ageing and sex/gender.
- Identification of barriers and facilitators to the involvement of different population groups in research.
- Further investigation of the susceptibility of older men to NSAID adverse events.
- Development of a 'register of registries and databases' and exploration of how linked health information systems in the UK could be improved.

Publication

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NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

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The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts. Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

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