Towards improving quality of the evidence base for medical decision-making

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Chapter 1

General introduction and thesis outline

Developments in the evidence base for medical decision-making

Research is a cornerstone of modern medicine. Since the late 20th century, medical practice has expanded from reliance on clinical expertise and experience to systematically integrating the best available research evidence to aid decision-making; a paradigm known as evidence-based medicine (EBM).[1,2] Over time, the evidence base informing medical decision-making has evolved. Scientific output in the life sciences is expanding at an exponential rate, with publication rates estimated to double approximately every 14 years.[3] This growth is largely driven by increasing numbers of biomedical researchers contributing to the field,[4] including clinician-investigators.[5]

Simultaneously, the availability of data has increased dramatically.[6] Patient health records, claims data, and prescription data have been digitised, alongside the rise of information from digital tools such as smartphones and wearable devices. These routinely collected types of data are often referred to as real-world data (RWD),[7] and although collected for other purposes than research, they provide opportunities to investigate important clinical questions.

A shift has also occurred in evidence generation for drug development. In the 20th century, pharmaceutical research predominantly focused on relatively simple chemical compounds targeting common diseases in broad populations (e.g., statins to reduce cholesterol levels and cardiovascular disease).[8] Evaluation of efficacy relied on large-scale randomised controlled trials (RCTs), widely regarded as the gold standard for assessing the efficacy of interventions. However in recent decades, drug development has increasingly shifted to more complex and targeted therapies, such as biologics and gene therapies. These treatments often address specific patient populations (e.g., rare diseases, mutation-specific targets), for which large-scale RCTs may be infeasible.[8] Consequently, alongside the increasing opportunities of RWD, the evidence base for evaluating drug efficacy is becoming more heterogeneous, including RCTs, alternative trial designs (e.g., basket trials, umbrella designs, platform trials), single arm trials, as well as real-world evidence (RWE) studies.

Challenges related to the evidence base for medical decision-making

Despite the rapid expansion of medical research, concerns have been raised regarding the reliability, reproducibility, and overall value of the generated evidence. It has been suggested that a substantial proportion of research findings are false.[9] Furthermore, it has been estimated that up to 85% of biomedical research funding is wasted throughout various stages in the research enterprise.[10] The factors that contribute to this problem are numerous and complex.

One challenge concerns the fragmented nature of medical research. New studies are often designed and conducted in isolation, with insufficient consideration of existing evidence or ongoing studies on the same topic.[11] This lack of coordination can result in redundant investigations, inefficient resource allocation, and underpowered studies.[12] For example, sample size determinations are rarely based on meta-analyses of prior evidence.[13] As a result, chosen parameters may be overly optimistic, leading to inadequate statistical power and thereby increasing the likelihood of inconclusive or misleading results. A similar problem occurs when studies discontinue before the target sample size is reached. About 25-30% of clinical trials discontinue prematurely, often due to preventable reasons such as recruitment failure,[14,15] contributing to research waste.

The increasing use of RWD introduces additional challenges. Since these data are collected for other purposes than research, they often suffer from measurement error, missing values, and a lack of important variables (e.g., confounders).[16] To draw valid inferences from these datasets requires advanced

epidemiological methods and rigorous study designs. Yet many researchers, including clinician-investigators, lack formal research training. This is particularly problematic because most effects of interest in modern medicine are relatively small, making it difficult to distinguish true effects from potentially biased results.[17] Unlike the 20th century, during which large effects (e.g., smoking and lung cancer) were identified, contemporary research increasingly involves marginal treatment benefits (e.g., comparing new treatments to existing treatments rather than placebos); a minor bias may therefore easily mask the true (direction of the) effect. A related challenge concerns the large flexibility in data analysis (sometimes referred to as "researcher degrees of freedom"), especially when study protocols are poorly documented or unavailable.[17] Combined with optimism bias and selective reporting,[18] this flexibility can lead to misleading conclusions and undermine the evidence base for medical decision-making.

Another issue contributing to research waste is the non-dissemination of study results.[19] While publication rates have improved, a substantial proportion of studies remain unpublished (despite the existence of trial registries), particularly those with negative or inconclusive findings, distorting the evidence base.[20] Underpowered studies might be especially at risk for publication bias, as they are more likely to miss clinically important effects and are typically of lower quality than larger studies.

Finally, an important challenge concerns the evaluation of medicines for market authorisation and reimbursement. Regulatory bodies (e.g., European Medicines Agency, Food and Drug Administration) assess efficacy and safety when judging market authorisation, while health technology assessment (HTA) bodies evaluate comparative effectiveness, safety, and cost-effectiveness for reimbursement decisions. The evidence base for informing these decisions – particularly regarding treatment efficacy and effectiveness – is shifting from large-scale, traditional RCTs with high internal validity, to a more heterogeneous mix, including RWE.[8] However, it remains unclear when RWE is desired or considered necessary by regulators and HTA bodies, and how different types of evidence should be weighed in decision-making.[21] As a result, market approval and reimbursement decision-making has become increasingly complex. Relatedly, sponsors may face uncertainties about when to conduct RWE studies, and where evidence requirements may differ or overlap between regulators and HTA decision-makers, potentially resulting in inefficiencies, unnecessary delays, and research waste.

Thesis aim and outline

The challenges related to the evidence base for treatment effectiveness and subsequent medical decision-making are numerous, and those described above are not exhaustive. This thesis aimed to address some of these challenges to improve the quality of the evidence supporting medical decision-making. We looked at various stages of the research enterprise.

Sample size calculations are an essential component of biomedical study design. **Chapter 2** provides a brief an overview of sample size estimation and common pitfalls. It is argued that a better understanding of the importance of adequate sample size calculations could protect against undesirable practices. For example, parameters for sample size calculations should be chosen to ensure that a meaningful difference can be reliably detected if such a difference exists. However, evidence suggests investigators often choose overly optimistic hypothesised effect sizes, increasing the chance of inconclusive results and research waste.[22] This phenomenon, and the role of research ethics committees (RECs) in evaluating sample size calculations and potentially mitigating optimism bias, is further investigated in **Chapter 3**. We compared sample size calculations across different protocol versions of RCTs submitted to a REC, and examined comments raised by REC reviewers regarding the sample size calculation during ethics review. We then compared the

hypothesised effects used in sample size calculations to the observed effects reported in corresponding publications, to assess whether ethics review and modifications to the sample size across protocol versions lead to more adequately powered studies.

Similar to studies that are designed with too small sample sizes, trials that discontinue prematurely due to preventable reasons such as recruitment failure, also contribute to research waste. In **Chapter 4** we identified potential predictors for early trial termination at the time of ethics review.

Small trials, which are often investigator-initiated and have limited resources, may be more prone to biases, and are notorious for being underpowered. They may also have a higher probability of non-publication. In **Chapter 5** we examined publication rates of small trials to quantify non-publication and identify factors associated with it.

RWE is increasingly submitted alongside the evidence from RCTs to regulatory authorities (e.g., EMA, FDA) and HTA bodies, to inform decisions on market approval and reimbursement. However, it is remains unclear when RWE is considered necessary by regulators and HTA decision makers, and how these different types of evidence should be weighed in decision-making. In **Chapter 6** and **Chapter 7**, we identified factors that increase the need for RWE in regulatory and HTA decision-making through literature reviews and stakeholder interviews, and compared these factors across the two domains. Clarifying the need for RWE could help determine the weight it should carry in decision-making, and inform when sponsors should conduct RWE studies that could satisfy evidence requirements from both regulators and HTA decision-makers.

Finally, **Chapter 8** reflects on the findings of this thesis and outlines directions for future research.

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