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Surrogate endpoints in trials—a call for better reporting

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Evidence for the effectiveness of interventions should ideally come from randomised controlled trials (RCTs) that assess a participant relevant final outcome, such as all-cause mortality.[1 2] However, such trials require large sample sizes, long follow-up times, and are ultimately costly.[2] One way to improve trial efficiency is the use of a surrogate endpoint that acts as proxy and predictor for the participant relevant final outcome.[3] Over the past 20 years, drug licensing in United States (US) and Europe has allowed the use of surrogate endpoints in the approval of new therapies, typically based on biomarkers e.g. systolic blood pressure and/or low-density lipoprotein cholesterol for cardiovascular death, HIV viral load for development of AIDS, and tumour response for overall survival.[3] However, it is important to acknowledge the potential application of surrogates in the wider setting of non-drug trials and the use of intermediate outcomes that may lie more distally on the causal pathway to a final outcome e.g. hospice enrolment for mortality with an intervention aimed at improving end of life care[4]; fruit and vegetable consumption for cardiovascular events for a behavioural intervention designed to improve cardiovascular risk.[5]

Despite their benefits, use of surrogate endpoints in evaluation and regulatory approval of health interventions remains highly controversial. First, some drugs, approved on the basis of surrogate endpoints, have failed to deliver improved participant relevant final outcomes, and in some cases, cause more overall harm than benefit, due to "off treatment-surrogate-final outcome pathway" effects.[6] A notable illustration is the diabetes drug rosiglitazone, approved by the US Food and Drug Administration (FDA) in 1999 and European Medicines Agency (EMA) in 2000 after a number of short term phase I-III clinical trials, showing that it improved the surrogate endpoints of blood glucose and glycosylated haemoglobin (HbA1c).[7] However, meta-analyses of RCTs published some 10 years later together with the large RECORD trial (4447 type 2 diabetes patients followed up for 6 years) with the primary outcome of cardiovascular hospitalisation or cardiovascular death, showed that the addition of rosiglitazone to standard drug therapy did not improve cardiovascular risk, and was associated with increased heart failure hospitalisation and a potential increase in myocardial infarction.[7] Following EMA reassessment, rosiglitazone was withdrawn from the UK market in September 2010. Furthermore, trials of surrogate primary outcomes trials have been shown to overestimate the health benefits of interventions by >40% (adjusted ratio of odds ratios: 1.46, 95% CI: 1.05 to 2.04), compared to trials using participant relevant final primary outcomes.[8]

Surrogate treatment effect overestimation has fundamental implications for payer/reimbursement organisations such as the National Institute for Health and Care Excellence (NICE) and may result in the funding and introduction of new therapies into healthcare systems that are not truly cost effective.[9] Therefore, it would be expected that RCTs using a primary surrogate endpoint pay close attention to this aspect of design in their reporting e.g., clearly stating that the primary outcome is a surrogate, outlining the rationale for its use, and providing evidence of the surrogate endpoint being on the causal pathway or its validity (e.g., meta-analysis of RCTs showing a strong association of the treatment effect on the surrogate endpoint and final participant relevant outcomes[10]). Unfortunately, this appears not to be the case; the most recent analysis, a review of RCTs published in 2005 and 2006, found that 17% (107/626) used a surrogate primary endpoint and of these, only a third discussed whether the surrogate endpoint was validated.[11]

Implementing reporting guidelines such as the widely used SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013[12] and CONSORT (Consolidated Standards of Reporting Trials) 2010 statements[13] can improve completeness of protocol and RCT reporting.[14] However, these guidelines and their extensions, including SPIRIT-PRO[15] and CONSORT-PRO[16]) and ongoing CONSORT-Outcomes,[17] do not directly address the issues of surrogate endpoint reporting.

Competing interests: We are working on a new initiative to develop guideline extensions specific to surrogate outcomes ('SPIRIT-SURROGATE' and 'CONSORT-SURROGATE') (https://www.gla.ac.uk/spirit-consort-surrogate). The aims of these extensions are to improve the reporting RCT protocols and reports that use a surrogate primary endpoint. None further declared.

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