TRIALS

Statistical evaluation of surrogate endpoints: a systematic review

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From 2nd Clinical Trials Methodology Conference: Methodology Matters
Edinburgh, UK. 18-19 November 2013

Background
Surrogate endpoints that can be used to predict treatment effect on an unobserved true endpoint are valued as their use may reduce the length, size or intrusiveness of a clinical trial. We aimed to update a previous systematic review on the theoretical statistical development of methods of validating surrogates for such a purpose.

Methods
We searched MEDLINE and Web of Knowledge, from Jan 2003 to Feb 2013, locating 12,762 papers. After preliminary screening, two independent reviewers assessed each paper and 88 were agreed to contribute to the statistical methodology of surrogate evaluation.

Results
Prentice's operational criteria, proportion of treatment effect explained and relative effect were the original techniques for evaluating surrogacy. These led to the development of several approaches for surrogate evaluation, namely; principal stratification, direct and indirect effects, meta-analytical (including the surrogate threshold effect) and information theory. Each methodological approach raises various computational issues in practice and conceptual issues regarding causality, transportability and interpretation.

Conclusions
In theory, the principal stratification and direct and indirect effects approaches may be considered most appropriate because of their ability to validate surrogates on a causal basis. However, in practice, the well-established meta-analytical and information theory approaches are currently in advance of other techniques mainly due to superior ease of interpretation and computational feasibility.

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