

STATISTICS COLLOQUIUM

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“Surrogate Measures and Consistent Surrogates”

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ABSTRACT

Surrogates which allow one to predict the effect of the treatment on an outcome from the effect of the treatment on the surrogate are of interest when it is difficult or expensive to measure the primary outcome. There have, however, been several instances of drugs that have been approved for use on the grounds of randomized trials using surrogate outcomes, that have subsequently led to public health catastrophes, costing thousands of lives. It is now clear that the use of surrogates can give rise to paradoxical situations in which the effect of the treatment on the surrogate is positive, the surrogate and outcome are strongly positively correlated, but the effect of the treatment on the outcome is negative, a phenomenon sometimes referred to as the "surrogate paradox." New results are given for consistent surrogates that extend the existing literature on sufficient conditions that ensure the surrogate paradox is not manifest. Specifically, it is shown that for the surrogate paradox to be manifest it must be the case that either there is (i) a direct effect of treatment on the outcome not through the surrogate and in the opposite direction as that through the surrogate or (ii) confounding for the effect of the surrogate on the outcome, or (iii) a lack of transitivity so that treatment does not positively affect the surrogate for all the same individuals for which the surrogate positively affects the outcome. The results are related to several common approaches and measures for assessing surrogacy including the "proportion explained" and the Prentice criteria, the "proportion mediated", meta-analytic approaches, and principal strata effects. None of these measures or approaches entirely protect against the surrogate paradox. An attempt is made to synthesize the existing approaches and results into guidelines on avoiding the surrogate paradox and ensuring consistent surrogates.