ESR Researcher Project: Non-technical Summary

"Incorporating preclinical information into phase I first-in-man trials"

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In early drug development, safety remains a key priority and special concern. Conventionally, phase I first-in-man trials are conducted on the basis of a dose-escalation procedure, which bases interim decision making on toxicity data accumulated from the ongoing human trial. However, no phase I clinical trials have been designed without preclinical studies characterising the toxicity profile of a new medicine in animals.

Borrowing of information from preclinical studies may potentially lead to more informed decisions, especially when the human data are sparse. The question is whether, and how, we can incorporate such preclinical data into a phase I clinical trial.

A challenge one faces when attempting to use preclinical information is whether it is commensurate with data accrued from the human trial. If, for example, preclinical and human toxicity data are consistent, augmenting the phase I clinical trial with animal data will result in improved estimation precision and more efficient decision process. However, such advantages must be balanced against the risk that more patients may be treated with excessively toxic doses when the drug is more toxic in humans than it is in animals.

We propose a new model for adaptive incorporation of preclinical data into a fully sequential phase I clinical trial. This approach is decision-theoretic, taking account of both advantage and ethical hazard that correspond to possible decisions of incorporating preclinical data. In order to borrow strength to an appropriate degree, preclinical data are used to make prior prediction of human toxicity outcome of the assigned dose. These predictions are optimal in the sense of maximising the prior expected utility. At each interim analysis these prior predictions are compared with the actual human toxicity outcomes. The attained predictive utility, expressed as a fraction of the maximum utility achieved when all prior predictions are correct, is then helping quantify the weight to be attributed to the preclinical data. We note that choosing suitable reward and penalty utilities requires expertise from clinicians and statisticians.

The proposed methodology is robust and responsive to potential conflicts between animal and human data. It allows the data to speak and, more importantly, supports ethical phase I trial designs: in situations where there is a clear discrepancy, our model discounts preclinical information quickly. In an extreme case that it has to be completely discarded, our methodology is reduced to a standard Bayesian model currently used for running phase I trial. Whereas, in cases of consistency, benefits are suggested to be more accurate characterisation of toxicity in humans and higher proportion of patients allocated to the target dose.

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Finally, we note our proposal can be applied more broadly: it discusses in general how historical information can be downweighted in relative to data from the new study and offers a feasible solution of formal incorporation to all relevant information.

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