Magnetic Resonance Metrics as Biomarkers

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Even the majority (90%) of molecules proposed as potential new drugs that enter "first time in human" studies do not survive as viable drugs over their decade long progression through evaluations in clinical trials. The high cost of clinical studies (particularly for important chronic diseases that show slow clinical progression) and this high rate of failure have led to an unsustainable cost for bringing new drugs to market. The pharmaceutical industry therefore looking to biomarkers to provide more efficient approaches for discharging key risks in drug development, especially early in the process before major investments in a molecule are made.

Key questions that need to be addressed include: 1. does the molecule reach the desired target (biodistribution)? 2. can a pharmacologically active concentration be achieved in the target tissue (pharmacokinetics)? 3.does interaction of the molecule with target have the hypothesised pharmacological effect (pharmacodynamics or "proof of mechanism") 4. is there evidence that the pharmacological effect leads to a desired clinical outcome ("proof of concept")? 5. will the molecule provide sufficient unique value relative to other treatments that payers will reimburse for its use (differentiation)?

A first characteristic of a good MR metric is that the objective can be well defined in terms of these key development questions. Clinical trials are complex and potentially expensive. They need to allow clear decisions to be made on the basis of their outcomes.

Application is predicated on the availability of data establishing the ***sensitivity*** and ***specificity*** of the metric. Considerations of sensitivity should address the potential to estimate changes in the range expected. For example, if an anti-cancer drug is expected to accumulate in tumours in concentrations ranging from 1-5 μM, conventional MRS would not be expected to be sufficiently sensitive. A related question concerns the variance or precision of the measures. How reliable an estimate can be made of the true value with feasible numbers of subjects? The specificity of the measure directly determines its interpretability. Are the factors that contribute to the metric well-defined? Understanding this is essential for information to be derived from the data. For a well-chosen metric, the higher the information content, the higher the potential to make meaningful decisions based on the measure.

Sensitivity and specificity reflect intrinsic qualities of the measure. It also is important to be able to define the ***clinical or pharmacological significance*** of any changes in the measure that are expected. Physicochemical or biochemical phenomenon determine MR signals most proximately. These need to be able to be able to be interpreted confidently in the context of the drug development application. Can a direct relationship between the expected pharmacology and a biochemical change measured by MRS be defined, for example? Can MRI lesion size changes in disease be correlated with clinical outcome measures in a way that gives a "reason to believe" in the potential for efficacy if desired changes in the former are seen?

A pragmatic distinction can be drawn between early and late phase trials for questions of significance. In addition to providing key safety and tolerability data, the former are conducted primarily to allow internal decision making before committing to the expense of a pivotal, late phase trial. An MR metric used for an early phase trial therefore needs only to achieve levels of sensitivity, specificity and contextual significance sufficient to raise confidence in a decision commensurate with the costs and time for execution. Qualification of the measure thus can be direct or indirect, depending on the application. However, for a late phase trial, MRI cannot be used to do more than enhance understanding or suggest hypotheses (e.g., for differentiation or new applications) unless the MR metric has achieved true surrogacy status- that is, changes in the measure have such an established direct relationship to clinical outcome that they can be used as a substitute for clinical measures. The hurdles for establishing surrogacy status are high and may be treatment class, as well as disease, specific.

There are additional general considerations for good metrics. The measure should be well-defined *a priori*. Exploratory methods can be powerful for generation of new pharmacological hypotheses, but provide a weak basis for decision making. A special strength of MR measures lies in their potential to be applied across both preclinical and clinical studies, allowing detailed development and qualification of methods translationally. Good metrics also should be robust to outliers, to different operators or observers and across sites applying them. For MR measures, issues of both data acquisition and analysis are relevant. Finally, the MR measure must be feasible given operational and cost constraints.