A brief proposal for improving clinical trials

AB Niculescu III,2,3

“What gets measured gets managed.”
- Peter Drucker

We have previously described a plan for discovering, prioritizing, validating and testing biomarkers1 and proven in practice how it works.2,3 It has not escaped our attention that our four-step approach could be transmuted for clinical trials. This approach takes a promising pre-clinical compound, developed against a specific molecular target or coming out of a screen, and runs it through its clinical phases.

Discovery would be Phase 1. It would involve a small number of ill individuals studied longitudinally, with testing before, during and after a very short course of drug administration, which may be repeated (off/on/off/on/off). If the drug is targeted against a specific mutation, the subjects enrolled would be carrier of that mutation. There would be a male group and a female group, as gender differences are profoundly important and much underappreciated. Whole-genome blood transcriptomic data (and possibly proteomic and metabolomics data) and whole-phenome data4 (quantitative clinical rating scales, imaging and electrophysiology) would be collected at every testing visit. Using a within-subject design, genes and phenes that change in expression, tracking the drug administration will be identified. Within-subject designs are more powerful than between-subject designs, thus, generalizable and reproducible signal can be obtained with much smaller cohorts. A within-participant design factors out genetic variability, as well as some other medications, lifestyle and demographic effects on gene expression, permitting identification of relevant signal with Ns as small as $10^1–10^3$.5,3 Another benefit of a within-participant design may be accuracy/consistency of self-report of symptoms (‘phene expression’), similar in rationale to the signal detection benefits it provides in gene expression. Thus, at the end of Phase 1, we would have candidate biomarkers for the drug, as well as an understanding of which phenotypes it may modulate (beyond the primary phenotype/diagnosis that it is being developed for) by gender.

Prioritization would be Phase 2. Subjects for this phase larger number and longer duration of treatment would be enrolled based on the primary phenotype/diagnosis/mutation the drug is being developed for, as ill patients vs normal controls. Studies will be conducted separately for men and women. They will be tested on a panel of the top biomarkers and top phenes from Phase 1, in addition to the primary outcome measures related to the primary phenotype/diagnosis/mutation the drug is being developed for. At the end of Phase 2, we will know which biomarkers and phenes are most changed in ill patients vs controls, and from those, which of them are best normalized by treatment, in each gender.

Validation would be Phase 3. Subjects for this phase would be enrolled in a targeted manner, based on the best biomarkers and phenes prioritized in Phase 2, in addition to or in lieu of the primary phenotype/diagnosis/mutation. If successful, the drug is then FDA approved along with companion diagnostic biomarkers and possibly monitoring devices/apps for the phenes.

Testing would be Phase 4, whereas, data from the drug’s use in the population at large continues to be analyzed. For example, the drug and companion diagnostic testing, devices and apps could be provided for free to independent cohorts of individuals, in different geographical locations, who agree to share their data with the pharmaceutical company or other entity conducting the clinical trial. This would show how reproducible the efficacy of the drug is, and may provide future insights into personalizing the treatment (time of administration, dosages, interactions with other medical conditions or lifestyle factors, by gender, age and possibly ethnicity).

The whole process would arguably be faster and safer, with a much higher likelihood of success or repurposing of a drug for a different phenotype/diagnostic/mutation indication. It may also be less expensive in the long run than current approaches, by reducing inefficiencies and wasted efforts. Starting with solid diagnostics first, and treatments that modulate it second, may promote a switch in our thinking from companion diagnostics to companion therapeutics.

CONFLICT OF INTEREST
The author declares no conflict of interest related to this work. ABN is listed as inventor on a patent application being filed by Indiana University.

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REFERENCES
