Reforming Clinical Trials in Drug Development: Impact of Targeted Therapies

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IT’S NOT JUST THE TRIAL, IT’S THE DEVELOPMENT PROGRAM
Success Depends Less on Novel Trial Design than on the Knowledge that Underpins the Program

• Understanding natural history—what will happen to people in the trial, and when?
• If you are using novel clinical endpoints, or standard endpoints in a new disease, how will they perform?
• What about PROs?
• Power calculations are not enough, you should model and simulate based on what you know, to see if design is feasible
Common Problems in Rare Diseases and Disease Subsets

• Natural history of the disease or disease subset not clear
  – For disease subset, includes prognosis compared to overall disease

• Biomarker measurements, their discriminatory performance, cutoffs, etc not well worked out

• Outcome measures for disease have never, or rarely, been tested

• Overall development plan not a whole

• Murphy’s law operates
So What’s a Developer to Do?

- Develop as comprehensive an idea of the natural history as possible
  - Involve patients
  - Do not simply consult experts on their experience
- Qualify all proposed biomarkers and outcome measures as thoroughly as possible, *before* starting to rely upon them
- Conduct a seamless, adaptive development program
Natural History of Disease: Critical to Planning a Development Program

• Burden of disease
  – What are the symptoms?
  – What would patients most like to have relieved?
  – Are there instruments to measure these?
  – Tradeoffs: how much risk is acceptable for benefits?

• Rate of progression of symptoms
  – Over what time period does measurable change occur?
  – What symptoms progress faster and is this true for everyone?
  – Don’t just rely on experts, they are usually wrong, due to sampling bias
Natural History

• Disease heterogeneity
  – Often, rare diseases are heterogeneous in their expression; rare subsets may or may not be
  – Introduces more variability, which is the bane of finding signal within noise
  – With highly variable disease, self controlled trials may be best

• Many natural history studies are done by academia through registries, etc. May lack documentation, may not be representative sample
Gathering Reliable Natural History Data

- Patient advocacy groups increasingly involved
- NORD, Genetic Alliance, others (FDA Orphan product grant) supporting efforts
- Usually any of these, or academic registries, will need bolstering to provide information adequate to intelligently design a development plan for an intervention
- Start well before product slated to enter clinical development—you need these data as early as possible
Conundrums with Existing Natural History Data

• Biomarkers rarely defined and measured rigorously
• Clinical outcomes rarely well described in uniform fashion
• Longitudinal followup may be limited
• Various forms of bias may be present in selection of patients who were followed—or patients with particular characteristics required for targeted therapy may not be identified
Biomarker Issues

• Development program may be centered around a predictive (of patient response) or prognostic (for patient selection), or pharmacodynamic (for assessing activity) biomarker

• The crucial biomarkers may not be reproducible, precise, accurate, or informative. Their operating characteristics may not be known and how to designate a “positive” response (e.g. a threshold or cutoff) may be unexplored
Biomarker Issues

• Relying on the performance of such a biomarker as the basis for a clinical development program is folly, in my view
• However, some pragmatic compromises must be made
• Biomarkers critical to a development program should be explored, in humans, as thoroughly as possible, prior to initiating human studies
• If the biomarker is to be used for a critical purpose, for example patient selection or pharmacodynamic readout, remaining uncertainty should be addressed as part of the development program, potentially using an adaptive design.
Trial Designs in the New Era
Development Program Clusters Based on Clinical Situation

- Rare, life-threatening disease with no good treatment, targeted therapy reasonably expected (perhaps from early data) to have large treatment effect (e.g., breakthrough drug). Similarly for biomarker-identified subset of life-threatening disease with no good treatment. (often oncology)

- In this situation may see
  - “Extended Phase 1 Cohort” approval
  - Endpoints (cancer): response rate, PFS
Very Rare Diseases: Examples of FDA Approvals

• Lumizyme for Pompe Disease: survival data from an international registry of infantile-onset disease
• Carbaglu: Plasma level ammonia reductions in a case series
• Cholbam for bile acid synthesis disorders: data on growth, survival and reduction in abnormal cholestatic markers in a case series
• Glucarpidase for MTX toxicity: data on approx. 20 patients from NIH treatment protocol
What did These have in Common?

• Highly plausible mechanistic hypothesis
• Natural history data on untreated patients
• Highly plausible biomarkers; most could be measured in a standard manner
• Serious unmet medical need
• Relatively large treatment effect
Development Programs for Ultra-Rare Diseases

• Performing standard clinical trial may be very difficult
• N-of-1 studies looking at disease trajectory (e.g., slopes of various declines pre and post rx) may be feasible. Start observational part early.
• Data from natural history may be helpful if treatment results in a convincing departure and disease not too heterogeneous
• Oncology: “basket” trials with biomarker defined targets across histologic diagnoses; NCI “MATCH” trial
• Emergencies: NIAID Ebola trial with adaptive design and Bayesian analysis
Rare, Serious Disease, Size of Treatment Effect Unknown

• You cannot plan for a huge treatment effect to wipe out all the other problems
• “Randomize the first patient” (maybe not the very first, but randomization is the key to efficiently finding if there is a treatment effect)
• Dose-finding can be randomized, adaptive, include placebo arm
• If you expect the need for longer duration of therapy needed to see effect, build in interim analyses, you need not lose that much alpha
Clinical Situation: Serious, Rare or Uncommon Disease with Existing SOC

Opportunity to randomize early without using placebo

• Will need to do comparative trial unless new therapy is of obvious “breakthrough” stature and SOC is not very good

• Master protocols trying to address:
  – LungMapp: NSCLC randomize all comers at 2nd line to a biomarker-defined therapy vs SOC. Screening trial to ID biomarker-drug pairs
  – I-SPY 2: Poorer Px breast cancer, screen biomarker-drug pairs in neoadjuvant setting, “graduate” to definitive adjuvant trial vs. SOC
Clinical Situation: Common Disease with SOC

• Expectation that new therapy will be at least as useful as existing therapy
  – Perhaps for intolerant patients
  – Perhaps better safety profile

Usually looking a 2 NI trials for efficacy

If intolerant patients, should document this before enrollment, if SOC has “failed” should document how
Biomarker Endpoints: Accelerated Approval

• If planning program: need to reach agreement that biomarker is “reasonably likely to predict clinical benefit”
• Then generate “substantial evidence” on effect on biomarker
• Randomization usually best design in this situation, given that biomarker effects are generally less persuasive than clinical effects
Use of Predictive Biomarker to Select Patients: Does it Discriminate?

• Current experience shows that target status often correlates with *magnitude* of treatment effect, but there is no cutoff (for continuous biomarker)

• If you want to have a large treatment effect, may utilize cutoff

• If you want to include all responding patients, might incorporate a randomized design stratified by biomarker status. You could model how to adaptively manage the cutoffs based on the incoming data to get to a sweet spot of response and biomarker positivity
Use of Real World Evidence (RWE)

• There are no hard and fast rules about how evidence is generated, with the exception of informed consent and patient privacy
• Settings can vary along a spectrum from the standard clinical trial setup to a pragmatic trial run in the healthcare system(s).
• There are trade-offs among data reliability, pragmatism, control of errors, safety, and other factors
• Clearly you don’t want to run a first-in-human trial in the real world setting, for example
FDA is Evaluating Use of RWE

- Clearly, we have approved drugs for rare diseases based on data from registry-like case series
- We are exploring how randomization would work in registry or healthcare settings
- We are collaborating with groups working to improve the validity of key data elements collected in the process of health care, e.g., HER
- We have spoken to many groups that are assembling oncology care data in various ways and hope to provide valid platforms for investigations
Use of RWE

• NIH “Collaboratory” carrying on trials in real world setting—up front investment with providers but with very low per-patient costs
• Neonatal consortium: neonatologists organizing clinical trial network for NICUs—patients already “fully wired”
• Conversations on carrying on randomized trials in more-organized health care settings—feasible, but more questions remain
Summary

• Trial designs, no matter how novel, will only be as good as the knowledge that underlies them.

• No matter how advanced the design, you may be in trouble if you have too many variables in play in your very expensive clinical development program:
  – Variability in disease expression or progression
  – Lack of specificity of dx, px, or predictive biomarkers
  – Unknown or poor performance of COA’s
  – PROs that don’t reflect the patient’s view of burden of disease

Advanced design won’t cure the above unless you actually build exploration of them into your trial.
Conclusion

• Targeted, personalized, or precision medicine approaches can deliver large treatment effects, making development easier.

• Adequately-performing diagnostic, prognostic and predictive biomarkers are key to enrolling the right patient population, and this is not as straightforward as was initially thought.

• Understanding the performance of COAs is critical to picking the right endpoints.

• All the above much more crucial, with a smaller treatment effect.