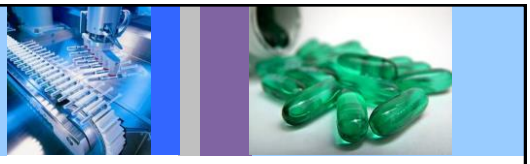

Challenges in Designing Pharmacogenomics Clinical Trials

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Clinical Genomic Analysis Workshop 2013

Outline

- PGx research questions
- Clinical trial designs
- Challenges

Goals of PGx research

- Investigating the contribution of genetic variation to inter-individual variability in response to drug treatment
- Promoting an optimal drug response for the individual patient

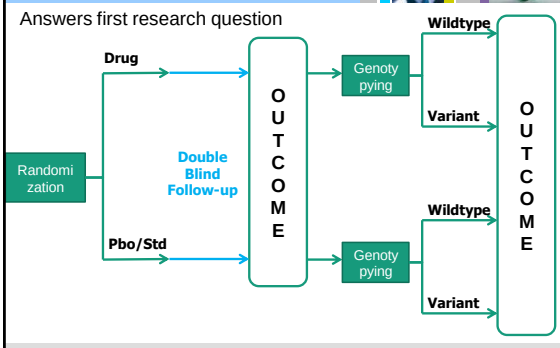
- Achieving better safety profile and mitigating potential risks
- Better understanding of MoA
- Identify disease genetics

Response related research questions

1. Does the treatment effect of the drug vary between subjects with different genotypes?
2. What is the benefit of the drug over placebo or an standard treatment for patients with a particular genotype?
3. What is the risk-benefit ratio of genotype-guided treatment over standard care?

Subgroups analysis design

Answers first research question



Subgroups analysis design advantages

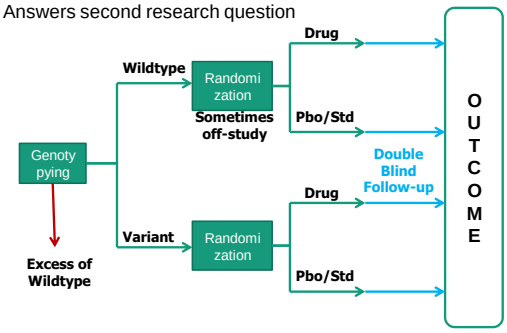
- Can piggyback on Phase II or III trial
- Simple, fast, relatively inexpensive
- Can test many genetic markers in one study
- Small chance of bias even where there are many genetic subgroups
- Provides efficient assessment of relative treatment efficacy in each genotype subgroup and in the whole group

Subgroups analysis design disadvantages

- Possible confounding bias
- Possible selection bias:
  - Some subjects may not consent
  - If DNA is not collected at baseline, clinical outcome may affect decision to consent
- Dependency of genotype distribution in the original study population
- Size of subgroups can't be controlled
  - Possible imbalance in baseline characteristics/ prognostic factors
  - Statistical power issues

Enrichment design

Answers second research question



Enrichment design advantages

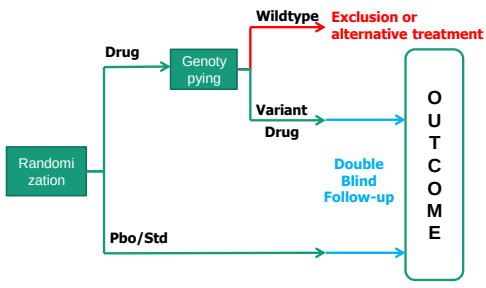
- Genotype strata can be balanced
- Can select subjects with genotypes between which the largest difference in treatment effect is expected (instead of all genotypes)
- Sample size and power calculation takes final analysis into account
- Selective consenting bias is avoided
- Opens door for possible adaptations

Enrichment design disadvantages

- "Tailored" study for particular genetic hypothesis
- Appropriate for contexts where there is such a strong biological basis for believing that "wildtype subjects" will not benefit from the new drug
- Efficient only when prevalence of variant is high and the effectiveness in variant population is high compared to the wildtype population

Genotype guided design

Answers third research question



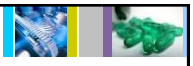
Genotype guided design advantages

- Assesses the added value of the PGx-based treatment over the current use of the drug and the corresponding costs
- Economic advantage of limiting the number of potentially expensive DNA genotypings
- Can be mimicked by a "regular" clinical trial, by comparing the whole treatment arm to its subgroup of "variant subjects" (statistical analysis is computationally intensive)

Genotype guided design disadvantages

- Inefficient in terms of sample size
- A positive study cannot distinguish between a successful treatment selection strategy and a situation in which the experimental drug is better than the control therapy for all patients

More to consider



- Adaptations: randomization, patient enrollment, enrichment, sample size re-estimation, group sequential design
- Combine general efficacy endpoint and PGx related endpoint in a single study – need to consider multiplicity issues

References

- van der Baan, F. H., Klungel, O. H., Egberts, A. C., Leufkens, H. G., Grobbee, D. E., Roes, K. C., & Knol, M. J. (2011). Pharmacogenetics in randomized controlled trials: considerations for trial design. *Pharmacogenomics*, *12*(10), 1485-1492.
- Freidlin, B., McShane, L. M., & Korn, E. L. (2010). Randomized clinical trials with biomarkers: design issues. *Journal of the National Cancer Institute*, *102*(3), 152-160.
- Simon, R. (2012). Clinical trials for predictive medicine. *Statistics in Medicine*, *31*(25), 3031-3040.
- Mandrekar, S. J., & Sargent, D. J. (2009). Clinical trial designs for predictive biomarker validation: one size does not fit all. *Journal of biopharmaceutical statistics*, *19*(3), 530-542.
- Trepicchio, W. L., Essayan, D., Hall, S. T., Schechter, G., Tezak, Z., Wang, S. J., Weinreich D., & Simon, R. (2006). Designing prospective clinical pharmacogenomic (PG) trials: meeting report on drug development strategies to enhance therapeutic decision making. *The pharmacogenomics journal*, *6*(2), 89-94.