

# The Challenge of Data Analysis and Integration in Current Transplantation and Immunosuppression Withdrawal Trials

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# Outline

- Based on my 30 yrs experience in clinical trials, including ~25 transplant trials, challenges in integration and analysis of data in transplant trials occur throughout the life of a trial:
  - Objectives
  - Endpoints
  - Study Design
  - Case Report Form Design
  - Specimen/Assay Management
  - *Integration of Clinical and Assay Data*
  - *Statistical Analysis*
  - Biomarker Profiling
  - Data Sharing

# Objectives

- A clinical trial protocol is very different from a grant application, where many transplant trials start
- Must translate scientific research objectives into clear clinical trials objectives that can drive a viable study design
  - Clinical trial protocol is the primary means of defining the trial and drives every aspect of its conduct
- Especially for IND trials, clearly define specific objectives with measureable outcomes for:
  - Safety
  - Efficacy
  - Mechanistic studies
- In particular, carefully pre-specified mechanistic hypotheses greatly simplify end of study analyses

# Endpoints

- Directly translate objectives into well-defined and reliable metrics of clinical and mechanistic outcomes
- If appropriate, surrogate endpoints must:
  - Be predictive of the clinical outcome
  - Fully capture effect of the intervention on the outcome
- Common clinical endpoints in transplant trials:
  - Acute rejection on biopsy
  - Tolerance in a IS withdrawal trial
  - IS dose reduction (or conversion) amount
  - Inflammation by histology
  - eGFR in kidney trials
  - Overall and allograft survival
- Composite endpoints are appealing can be difficult to justify if they haven't been used before

# Endpoints (continued)

- Clinical vs biopsy-proven acute rejection
- Protocol-mandated vs standard of care biopsies
- Direct measurement vs calculated (eg GFR)
- Continuous vs categorical (reality-based)
- Single vs repeated measures (eg change from baseline)
- Incidence vs time to event (frequently both)
- Central vs local assessments (cost vs variability)
- Specifying mechanistic endpoints helps clarify the study objectives and focus the analysis plan

# Study Design

- Limited choices for transplant trials essentially exclude:
  - Crossover designs, since usually can't sequence regimens
  - Adaptive designs, due to long-term endpoints
- Randomization for induction or maintenance therapy trials but frequently not for ISW trials
  - May consider unbalanced randomization to treat more subjects
  - Dynamic randomization to balance baseline features
- Usually involve parallel group designs with follow-up post-transplant up to 12, 24 months:
  - Cross-sectional clinical endpoints
  - Repeated measures clinical endpoints
  - Repeated measures of mechanistic assay endpoints
- Carefully design SOE to follow objectives and endpoints
  - Conditional follow-up schedules make life complicated

# Study Design (continued)

- Sample size considerations should not be a mystery:
  - Simply put,  $N = 1/F(\text{Signal/Noise})$  for specified alpha, beta
    - Frequently based on incidence rates, means, odds ratios
  - Requires estimates of expected effect and variance
  - Preliminary data is optimal but not always available
    - Speculate about standardized effect sizes
  - Frequently driven by realities of subject availability
  - Realistic estimate of dropouts to inflate N
  - Formal calculations required for primary clinical endpoints and recommended for primary mechanistic endpoint
  - How many subjects do I need?
    - As many as you can afford with acceptable error rates

# Clinical Data Management

- Good eCRF design is critical to good data analysis:
  - Only collect what you will analyze
  - Constrain data entry, avoiding free text
  - Simplify data collection for complex events
    - Detailed dosing data on IS drugs, but not con-meds
    - Limit biopsy and rejection data to easily gradable metrics
- Current EDC systems capable of real-time data QC:
  - Univariate, multivariate, cross-page edit checks
  - Reports on completeness of data entry by site and type
- Integrate closely with site monitoring to improve efficiency
  - Comprehensive and continuous data quality review

# Specimen/Assay Management

- Effective specimen management is critical to the success of the mechanistic objectives
  - Otherwise, risk having insufficient N for biomarker profiling
- Consider specimen tracking software using barcodes
- Need clear agreements with central assay labs
  - Essential to getting complete reliable results
- Carefully pre-specify data collection formats
  - Include specimen QC checks
  - Clarify units of measurement
  - Agree on imputation/normalization procedures, if needed
- Assay data usually collected outside the clinical EDC process

# Integrating Clinical-Assay Data

- Reconciliation of clinical-specimen-assay data can be a nightmare, with independent data collection sources
  - Single most effort-intensive DM task is to reconcile discrepancies between three data sources
  - Linked on subject, specimen type and visit identifiers, which are subject to error in spite of best efforts
  - Recommend integrating data collection as much as possible, can be expensive but well worth it in the end
- Ideal of collecting all clinical and assay data in one EDC system is probably not possible
  - Direct data entry incompatible with lab workflows
  - Combine specimen tracking and assay data collection
  - Allow for batch transfer and QC of assay results files

# Statistical Analysis

- Write a complete SAP early on, describing all analysis plans
  - Especially important for mechanistic assay data analyses
  - Include visualization/exploration steps to understand the data
  - In contrast to typical end of study batch analysis process
- Recognize potential multiple comparisons problems
  - Multiple endpoints are usually OK
  - Pair-wise comparisons of multiple groups and
  - Repeated measures over time are not
- Parametric vs non-parametric methods
  - Log transformation works well with most quantitative assay data
- Will frequently require use of complex analysis methods:
  - Mixed models for longitudinal data analysis of continuous variables
  - Generalized Estimating Equations (GEE) models for binary outcomes

# Biomarker Profiling

- Prediction of clinical outcome (eg BPAR) from potentially hundreds-thousands of candidate mechanistic parameters
- Three common analysis objectives:
  - **Diagnosis** of current outcome with non-invasive surrogate
  - **Prediction** of future outcome from longitudinal profile
  - **Response** to intervention (before and) after treatment
- General approach to mechanistic assay data analysis:
  - Dimensional reduction (eg principal components)
  - Univariate comparisons between outcome groups for screening
  - Classification model fitting and variable selection
    - Clustering, discriminant function, logistic regression, multiple regression
  - Receiver Operating Characteristic (ROC) curves
    - Quantify prediction error rates and calibrate cutoffs
  - Internal model validation by bootstrap re-sampling
    - More efficient than split sample cross validation with training and validation sets

# Data Sharing

- Required of NIH funded basic and clinical research with > \$500K/year in direct costs
  - [http://grants.nih.gov/grants/policy/data\\_sharing/](http://grants.nih.gov/grants/policy/data_sharing/)
- Most misunderstood requirement in grant applications and frequently ignored entirely
- Has nothing to do with sharing information among the collaborating study investigators during the trial
- During the trial, report results to *clinicaltrials.gov* when available
- After completion of the trial and release of primary publications, the investigators must have a plan to:
  - Fully de-identify linkable clinical and assay data sets
  - Document the clinical trial and all study data
  - Make data available to the public, typically on a website like <https://www.import.org/importWeb/home/>

# General References

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- International Conference on Harmonization guidelines for IND trials  
<http://www.ich.org/home.html>

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  - CTOT – Clinical Trials in Organ Transplantation
  - CTOT-C - Clinical Trials in Organ Transplantation in Children
  - GTCRP – Genomics of Transplantation Cooperative Research Program
  - ITN – Immune Tolerance Network
  - iWITH – Sandy Feng II

# Conclusion

In the end, if you have followed my advice and run a successful trial and established a viable biomarker, you get to do it all over again in the next trial in which you may pre-select subjects with the biomarker for a targeted intervention or ISW trial

# Questions?