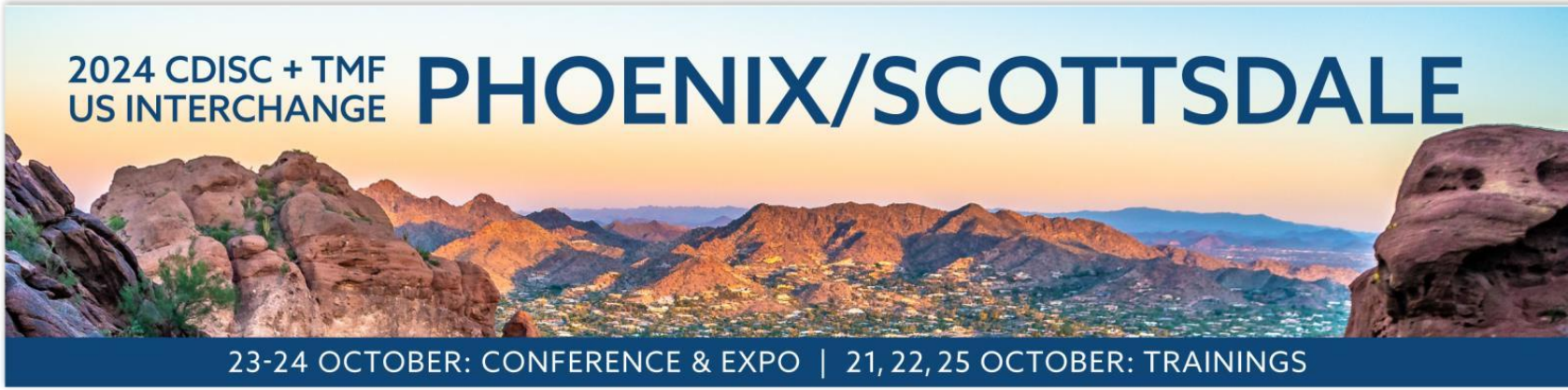
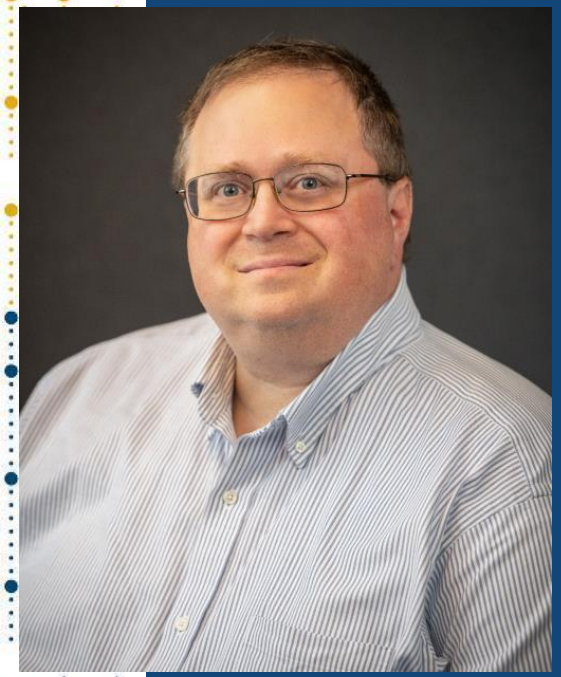


Food Allergy Research with CDISC Standards

Presented by Dave Scocca, Principal Statistical Programmer, Rho, Inc.



Meet the Speaker

Dave Scocca

Title: Principal Statistical Programmer

Organization: Rho, Inc.

In 25 years at Rho, Dave has been involved in many different kinds of programming. He currently specializes in producing SDTM datasets and submission packages.

Dave is a volunteer on the CDISC SDS and SDTM teams.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of CDISC.*
- *Research described here was supported by divisions of the National Institutes of Health under award numbers UM2AI130836-01, UM2AI117870 and 1U01AI178772. Nothing in this presentation represents any policy or position of NIH or any subdivision thereof.*
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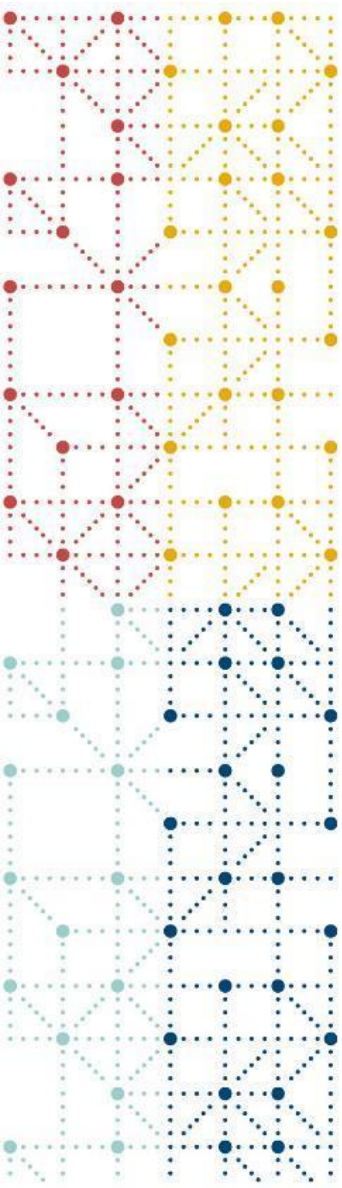


Agenda

1. Food Allergy Research
2. Data Collection and Tabulation
3. Analysis
4. Conclusions

Research Structure

- Consortium for Food Allergy Research (COFAR)
  - National Institute of Allergy and Infectious Diseases (NIAID)
  - Division of Allergy, Immunology, and Transplantation (DAIT)
- Rho Federal Systems Division
  - Studies typically conducted for scientific publication, not agency submission
  - Analysis data usually created directly from raw clinical data, without tabulation

OUtMATCH

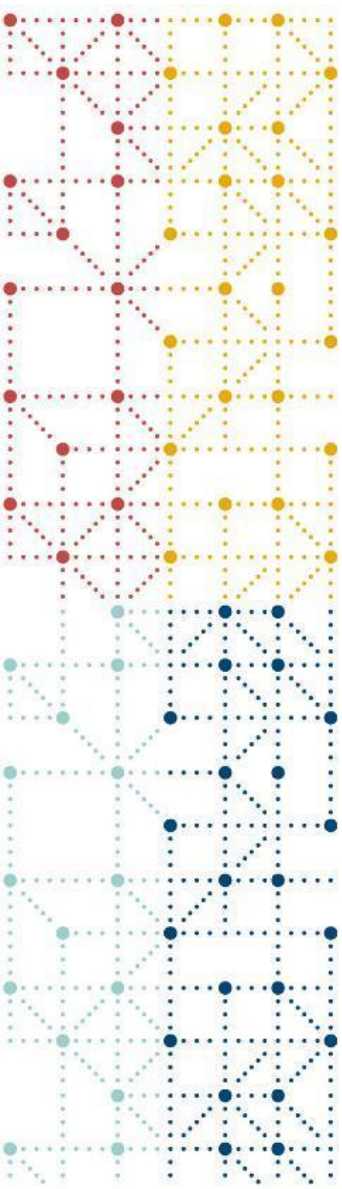
- Food Allergy Research
  - Food allergies have become more common
  - Severe anaphylactic reactions
  - Plenty of room for improved treatments
- Oral Immunotherapy (OIT)
  - Usually specific to a single food
  - Tiny doses can produce severe reactions
- Overall study plan:
  - Treat with an immunoglobulin G1 (IgG1) monoclonal antibody to reduce allergic reaction. This is a commercial product already approved for other indications.
  - Extend into multi-allergen OIT treatment to provide long-term benefits
- “Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Participants (OUtMATCH)”

Double-Blind Placebo-Controlled Oral Food Challenge

- Series of challenges
  - One or more potential allergens
  - One challenge is with placebo (oat)
  - OUtMATCH did sets of four, with additional screening sets as needed
  - Peanut plus two of Milk, Egg, Wheat, Cashew, Hazelnut, Walnut
- Dose escalation
  - Sequence of doses: 1mg, 3mg, 10mg, 30mg, 100mg, 300mg, 1000mg, 2000mg
  - Delay of at least 15 minutes between doses
  - Screening only goes up to 300mg, 100mg for peanut
  - 2000mg could be repeated two or three times depending on study period
- Assess symptoms
  - Dose-limiting symptoms (moderate or severe) identified in protocol
  - Monitor for 2 hours after last dose

Study Design of Drug Treatment Portion

- Screening
  - Food challenges to verify allergies and determine participant-specific foods (peanut +2)
  - Challenges unblinded after panel is completed.
- Blinded Treatment
  - Treatment with drug or placebo
  - Ends with panel of four food challenges to assess efficacy
- Unblinded Treatment
  - Open-label Extension (first 60 treated subjects)
    - Treatment period with open-label drug
    - Ends with additional panel of four food challenges
  - Study Phase 2 (subsequent subjects)
    - Begins with open-label treatment period
    - Continues to combination of drug and oral immunotherapy or placebo
    - No additional food challenges for just drug



Data Collection and Tabulation

Food Challenge Data Collection

- Each challenge is a separate day and a separate study visit (1-4)
- Blinded entry of which food was consumed at which challenge
- Three CRF modules
  - Food challenge summary (one form per challenge/visit)
    - Did subject meet requirements?
    - Was challenge performed?
  - Details of challenge (one form per challenge/visit)
    - Date, start and end times
    - Amount consumed
    - Result (positive/negative)
    - List of symptoms exhibited
  - Food challenge materials (one form per set of challenges)
    - Restricted to unblinded personnel
    - Which food was given in each challenge?

Data Collection: Food Challenge Summary

- Prerequisites for challenge
  - Antihistamine use
  - Recent food consumption
- Was challenge performed?
  - Why not?
  - Will it be rescheduled?

- Challenge mapped to a procedure in PR with occurrence in PROCCUR
- Prerequsites and rescheduling mapped to findings about procedure in FAPR
- Relationship between PR and FA documented in RELREC

Data Collection: Food Challenge

- Date, start time, and end time of challenge
- Cumulative dose consumed
- Cumulative dose without dose-limiting symptoms
- Overall result - positive (dose-limiting symptoms) or negative (no DLS)
- Symptoms (one line per reported symptom)
  - Symptom (pre-specified list, plus other, specify)
  - Onset time
  - Associated dose
  - Severity
  - Idenfity as dose-limiting and/or meeting adverse event criteria
- Treatment for symptoms
  - Pre-specified treatments plus other, specify

Tabulation: AG and FAAG

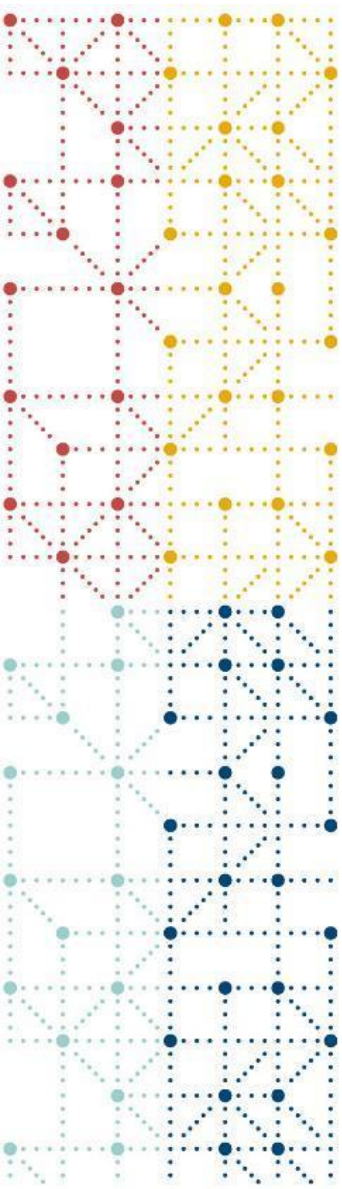
- AG (Procedure Agents) stores time and dose of food protein
  - AGTRT is blinded or based on scrambled data until panel of challenges is unblinded
  - AGDOSE is cumulative amount consumed
- FAAG stores findings about the exposure to the food protein
  - Cumulative dose without dose-limiting symptoms
  - Overall result (positive/negative)
  - Whether test was stopped prematurely
- FAOBJ = AGTRT
- Relationships in RELREC:
  - Protein exposure in AG and results in FA
  - Challenge record in PR and exposure record in AG

Tabulation: CE and CM

- CE (clinical events) lists all symptoms recorded
  - Symptoms meeting adverse event criteria were additionally recorded on AE form
  - SUPPCE fields for dose, DLS flag, and AE flag
  - RELREC associates symptoms in CE with protein exposure in AG
- CM stores medication responses
  - CMOCCUR for each type of medication (epinephrine, antihistamine, corticosteroid)
  - All dosing recorded separately on pages for epinephrine use or general medications
  - RELREC associates medications in CM with protein exposure in AG

Tabulation: RELREC

- RELREC is doing a lot of the heavy lifting for traceability
- All records in RELREC are for dataset-level relationships



Analysis

Analysis: Begin with the Endpoints

Most endpoints, including the primary endpoint and key secondary endpoints, were one of two types:

- Single-food endpoints
  - Consumption of a single dose of >= AMOUNT of FOOD NAME protein without dose-limiting symptoms
  - Consumption of [two or three] 2000mg doses of FOOD NAME protein without dose-limiting symptoms
- Multiple-food endpoints
  - Consumption of a single dose of >= AMOUNT of at least [two or three] different food proteins without dose-limiting symptoms
  - Consumption of [two or three] 2000mg doses of at least [two or three] different food proteins without dose-limiting symptoms

Analysis: Single Foods in ADOFC

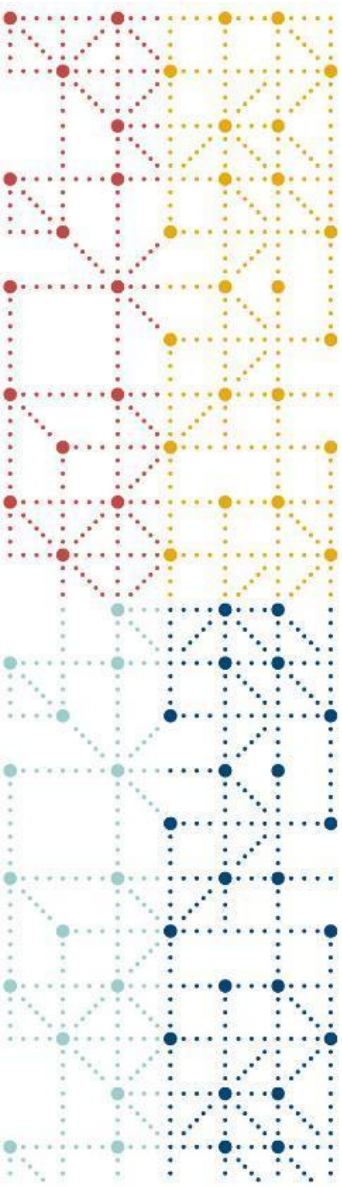
- One set of records per expected food challenge
  - Worst-case imputation if food challenge did not occur
- PARAM combined:
  - Food (Peanut, Milk, Egg, Wheat, Cashew, Hazelnut, Walnut, Placebo/Oat) from FAOBJ
  - Result:
    - Cumulative dose tolerated (from FAAG, cumulative dose without DLS)
    - Maximum dose tolerated (derived from cumulative dose tolerated)
    - Number of 2000mg doses tolerated (derived from cumulative dose tolerated)
- Orthogonal PARCAT groupings
  - PARCAT1 contained name of food
  - PARCAT2 contained type of result
  - Easy to write specifications, to program, and to document in Define-xml

Analysis: Single Foods Criteria ADOFC

- Analysis criterion flags used to support endpoint detection
  - CRIT1, CRIT2, and CRIT3 flags populated for maximum tolerated dose rows at three different dose amounts. CRITyFL set to Y if AVAL > amount for a valid test, N otherwise
  - CRIT4 and CRIT5 populated for number of 2000mg dose rows, with target of two or three. CRITyFL set to Y if number of doses matched target, N otherwise
- Each single-food endpoint could be assessed against a single CRITyFL field by subsetting on PARCAT1 (food)

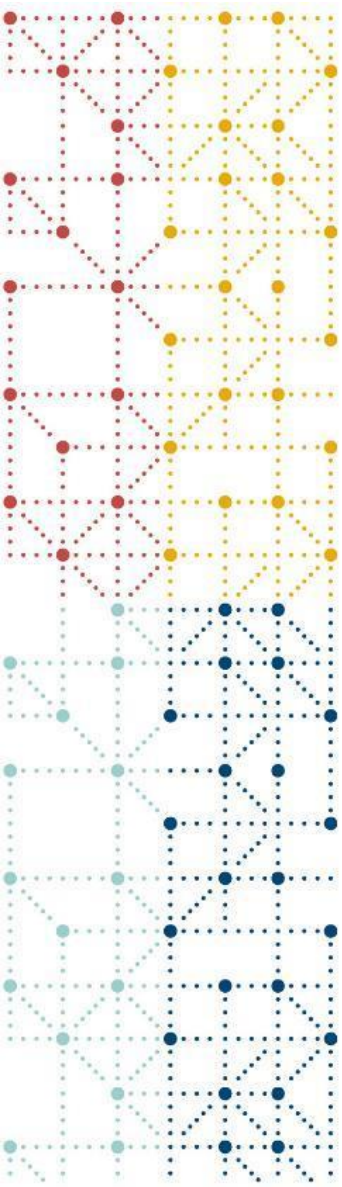
Analysis: Multiple Foods in ADOFCSUM

- ADOFCSUM derived from ADOFC
- One set of records per study period per criterion in ADOFC
  - PARAM was “Number of foods [meeting criterion]” based on ADOFC.CRITy
  - AVAL was sum of numeric criterion flags ADOFC.CRITyFN for study period
- Each multiple-food endpoint could be assessed against a single CRITyFL field in ADOFCSUM



Conclusions

- CDISC standards helped a lot
- Statisticians not used to tabulation appreciated SDTM
- Documenting relationships with RELREC is important
- Let ADaM do the heavy lifting
- Lesson learned: make CRF consistent with endpoints



Thank You!

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