The Role of the Statistician in Clinical Research Teams

Clinical trials in East Africa
Skills-sharing workshop

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Dan Kajungu Msc,

President – International Biometric Society, Group Uganda (Gugan)

The International Biometric Society GROUP UGANDA (GUgan)

STATISTICS2013.ORG INTERNATIONAL YEAR OF STATISTICS

IBS - Uganda group (GUgan)

- Current membership in Ug - 14 professionals
- Revived in May 2012
- Membership of $14 is paid directly to IBS
- Elected committee – President, Treasurer and Secretary
- Open for collaborations with both local and international groups
- A number of activities are planned for 2013
- We welcome anyone who is interested to join

For more details *http://www.biometricsociety.org*

Uganda Group contact: kajungu_dan@yahoo.co.uk

Statistics

- Statistics is the art/science of **summarizing data**
- Better yet…summarizing data so that non-statisticians can understand it
- Clinical investigations usually involve collecting a lot of data.
- But, at the end of your trial, what you really want is a "punch-line:"
  - Did the new treatment work?
  - Are the two groups being compared the same or different?
  - Is the new method more precise than the old method?
- Statistical inference is the answer!

Do you need a statistician as part of your clinical research team?

- YES!
- Simplest reasons: s/he will help to optimize
  - Design
  - Analysis
  - Interpretation of results
  - Conclusions

What if I already know how to calculate sample size and perform a t-test?

- Statisticians might know a better approach
- Trained more formally in design options
- Tend to be less biased
- Adds credibility to your application
- Use resources that are available to you

Different Roles

- Very collaborative
  - Active co-investigator
  - Helps develop aims and design
  - Brought in early in planning
  - Continues to input throughout trial planning and while study continues

- Consultants
  - Inactive co-investigator
  - Often not brought in until either
    - You need a sample size calculation several days before submission
    - Trial has been criticized/rejected for lack of statistical input
    - You've finally collected all of the data and don't know what to do next.
  - Only involved sparsely for planning or for analysis.

Find a statistician early

- Your trial can only benefit from inclusion of a statistician
- Statisticians cannot rescue a poorly designed trial after the trial has begun.
- “Statistical adjustment” in analysis plan does not always work.
- Ignorance is not bliss:
  - Some clinical investigators are trained in statistics
  - But usually not all aspects!
  - Despite inclination to choose a particular design or analysis method, there might be better ways.

Statisticians: Specific Responsibilities

- Design
  - Choose most efficient design
  - Consider all aims of the study
  - Particular designs that might be useful
    - Cross-over
    - Pre-post
    - Factorial
  - Sample size considerations
  - Interim monitoring plan

Statisticians: Specific Responsibilities

- Assistance in endpoint selection
  - Subjective vs. objective
  - Measurement issues
    - Is there measurement error that should be considered?
    - What if you are measuring pain? QOL?
  - Multiple endpoints (e.g. safety AND efficacy)
  - Patient benefit versus biologic/PK endpoint
  - Primary versus secondary
  - Continuous versus categorical outcomes

Statisticians: Specific Responsibilities

- Analysis Plan
  - Statistical method for **EACH** aim
  - Account for type I and type II errors
  - Stratifications or adjustments are included if necessary
  - Simpler is often better
  - Loss to follow-up: missing data?

Sample Size and Power

- The most common reason we get contacted
- Sample size is contingent on design, analysis plan, and outcome
- With the wrong sample size, you will either
  - Not be able to make conclusions because the study is “underpowered”
  - Waste time and money because your study is larger than it needed to be to answer the question of interest
- And, with wrong sample size, you might have problems interpreting your result:
  - Did I not find a significant result because the treatment does not work, or because my sample size is too small?
  - Did the treatment REALLY work, or is the effect I saw too small to warrant further consideration of this treatment?
  - This is an issue of CLINICAL versus STATISTICAL signficance

Sample Size and Power

- Sample size ALWAYS requires the investigator to make some assumptions
  - How much better do you expect the experimental therapy group to perform than the standard therapy groups?
  - How much variability do we expect in measurements?
  - What would be a clinically relevant improvement?
- The statistician CANNOT tell you what these numbers should be (unless you provide data)
- It is the responsibility of the clinical investigator to define these parameters

Sample Size and Power

- Review of power
  - Power = *The probability of concluding that the new treatment is effective if it truly is effective*
  - Type I error = *The probability of concluding that the new treatment is effective if it truly is NOT effective*
  - *(Type I error = alpha level of the test)*
  - *(Type II error = 1 – power)*
- When your study is too small, it is hard to conclude that your treatment is effective

Not always so easy

- More complex designs require more complex calculations
- Usually also require more assumptions
- Examples:
  - Longitudinal studies
  - Cross-over studies
  - Correlation of outcomes
- Often, “simulations” are required to get a sample size estimate.

Most common problems seen in study proposals when a statistician is not involved

- Outcomes are not clearly defined
- There is not an analysis plan for secondary aims of the study
- Sample size calculation is too simplistic or absent
- Assumptions of statistical methods are not appropriate

Examples:
trials with additional statistical needs

- Major clinical trials (e.g. Phase III studies)
- Continual reassessment method (CRM) studies)
- Longitudinal studies
- Study of natural history of disease/disorder
- Studies with ‘non-random’ missing data

Major trials

- Major trials usually are monitored periodically for safety and ethical concerns.
- Monitoring board: Data (Safety and) Monitoring Committee (DMC or DSMC)
- In these, trials, ideally you would have three statisticians (Pocock, 2004, Statistics in Medicine)
  - Study statistician
  - DMC statistician
  - Independent statistician
- Why?
  - Interim analyses require “unbiased” analysis and interpretation of study data.
- Industry- versus investigator-initiated trials …differences?

Study Statistician

- Overall statistical responsibility
- Actively engaged in design, conduct, final analysis
- Not involved in interim analyses
- Want them to remain ‘blinded’ until the study is complete

DMC Statistician

- Experienced trialist
- Evaluate interim results
- Decide (along with rest of DMC) whether trial continues
- No conflict of interest

Independent Statistician

- Performs interim analysis
- Writes report of interim analysis
- No conflict of interest
- Only person to have full access to “unblinded” data until trial completion

High-maintenance trials

- Some trials require statistical decision-making during the trial
- Simon “two-stage” design:
  - Stage 1: Treat about half the patients.
  - Stage 2: If efficacy at stage 1 meets some standard, then enroll the remainder of patients
- “Adaptive” and “Sequential” trials: final sample size is determined somewhere in the middle of the trial
- Continual Reassessment Method…

CRM history in brief

- Originally devised by O'Quigley, Pepe and Fisher (1990) **where dose for next patient was determined based on responses of patients previously treated in the trial**

- Due to safety concerns, several authors developed variants
  - Modified CRM (Goodman et al. 1995)
  - Extended CRM [2 stage] (Moller, 1995)
  - Restricted CRM (Moller, 1995)
  - and others….

Longitudinal Studies

- Multiple observations per individual over time
- Sample size calculations are HARD
- But, analysis is also complex
- Standard assumption of “basic” statistical methods and models is that observations are independent
- With longitudinal data, we have “correlated” measures within individuals

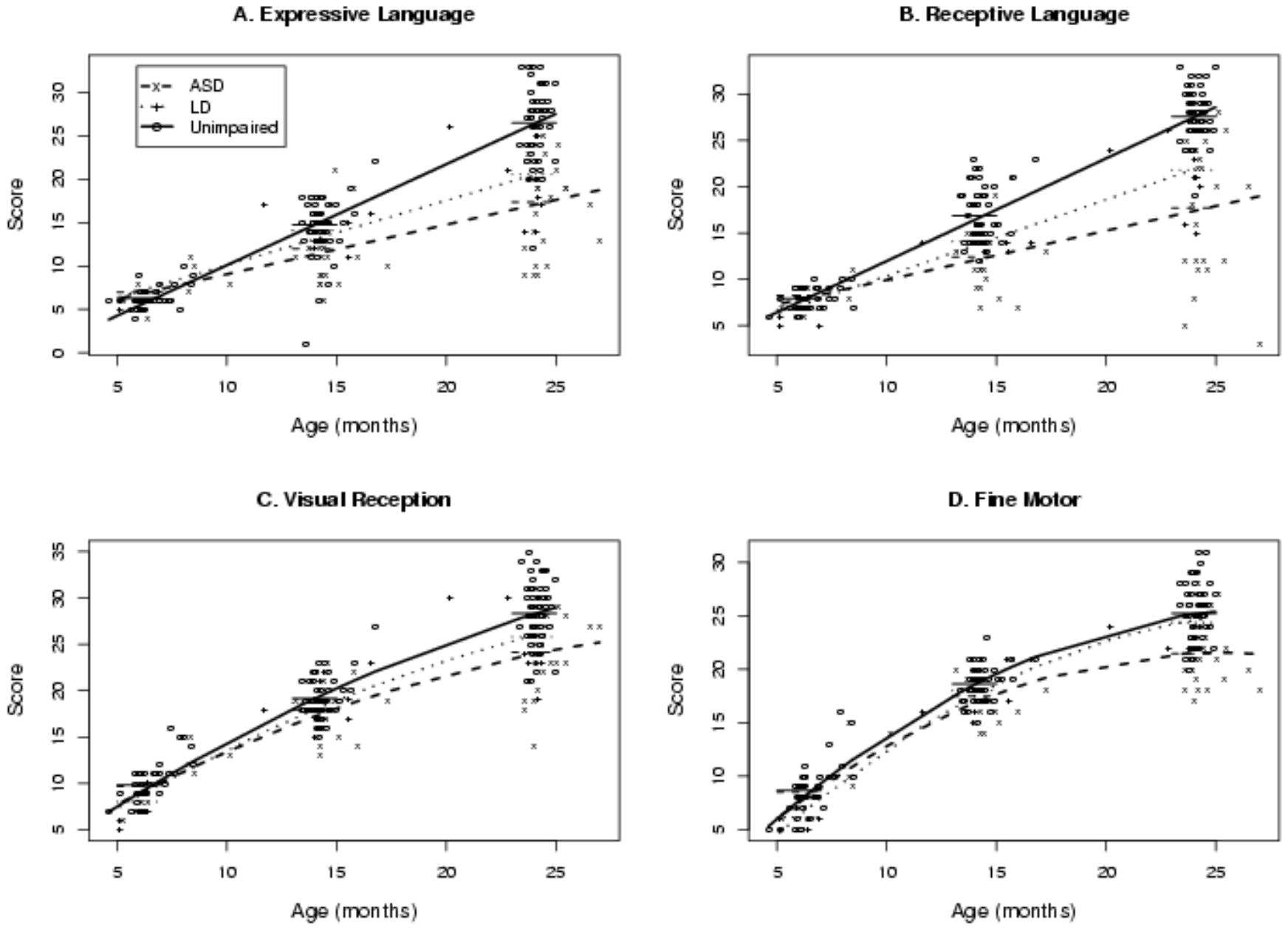
Study of Autism in Young Children (Landa)

- Autism usually diagnosed at age 3.
- But, there is evidence that there are earlier symptoms that are indicative of autism
- Children at high risk of autism (kids with older autism siblings), and “controls” were observed at 6 months, 14 months, and 24 months for symptoms (Mullen)
- Prospective study
- Children were diagnosed at 36 months into three groups.
  - ASD (autism-spectrum disorder)
  - LD (learning disabled)
  - Unaffected
- Earlier symptoms were compared to see if certain symptoms could predict diagnosis.

	ASD (n=23)		LD (n=11)		Unaffected (n=53)	
Mullen Subscales	Mean	(SD)	Mean	(SD)	Mean	(SD)
			6 Months			
Gross Motor	51.50	(7.69)	53.86	(6.31)	49.35	(10.35)
Visual Reception	52.58	(8.94)	47.43	(10.75)	55.18	(10.66)
Fine Motor	46.92	(11.86)	36.86	(7.45)	49.54	(10.76)
Receptive Language	50.75	(8.21)	44.86	(8.95)	50.18	(7.26)
Expressive Language	47.25	(10.14)	44.57	(4.57)	43.98	(6.70)
Early Learning Composite	100.67	(12.75)	87.29	(9.16)	99.59	(10.10)
			14 Months			
Gross Motor	46.91	(12.34)	52.91	(10.38)	58.16	(10.52)
Visual Reception	48.39	(10.95)	51.00	(9.32)	54.73	(9.03)
Fine Motor	50.48	(10.44)	52.82	(9.40)	57.41	(7.28)
Receptive Language	34.70	(13.38)	39.64	(5.95)	52.59	(12.26)
Expressive Language	39.04	(15.14)	47.00	(7.64)	52.02	(11.33)
Early Learning Composite	87.39	(19.97)	95.55	(10.68)	108.27	(13.89)
			24 Months			
Gross Motor	35.43	(8.69)	49.18	(11.04)	52.20	(10.97)
Visual Reception	43.26	(10.98)	48.91	(11.59)	56.73	(10.48)
Fine Motor	36.04	(14.17)	48.91	(7.97)	52.78	(11.07)
Receptive Language	35.74	(15.25)	42.73	(11.31)	59.22	(10.74)
Expressive Language	36.65	(15.31)	45.27	(12.03)	60.14	(12.15)
Early Learning Composite	78.43	(21.68)	93.73	(14.86)	114.98	(15.89)

Statistical modeling can help!

- Previous table was hard to make conclusions from
- Each time point was analyzed separately, and within time points, groups were compared.
- Use some reasonable assumptions to help interpretation
  - Kids have “growth trajectories” that are continuous and smooth
  - Observations from within the same child are correlated.


A. Expressive Language
B. Receptive Language
C. Visual Reception
D. Fine Motor
ASD
LD
Unimpaired
Score
Age (months)

Conclusions are much easier

- The models that were used to make the graphs as somewhat complicated
- But, they are “behind the scenes”
- The important information is presented clearly and succintly
- ANOVA approach does not “summarize” data

Concluding Remarks

- **Get your statistician involved as soon as you begin to plan your study**
- Things statisticians do not like:
  - Being contacted several days before grant/protocol/proposal is due
  - Rewriting inappropriate statistical sections
  - Analyzing data that has arisen from a poorly designed trial
- Statisticians have a lot to add
  - “fresh” perspective on your study
  - Study will be more efficient!