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Can We Get There? Re-Thinking Clinical Trial Design

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Disclosure

I am on speakers bureaus for Sanofi and Novartis and a DSMB for BMS.

Innovation for Clinical Trials in Transplantation

- Trial design
- Trial analyses
- Endpoints, endpoints, endpoints

Trial design

- Pragmatic clinical trials
  - "Real world experiences"
    - More likely to translate into practice
    - Increased external validity
  - Resource efficient
  - Engage numerous stakeholders
    - Health systems
    - Hospitals
    - Patients
  - Can be challenging for analysis

Adaptive designs

- Evaluates outcomes on an a priori prescribed schedule
- Allows for the opportunity to alter study design based on intermittent findings
  - Enrollment estimates
  - Inclusion/Exclusion criteria
  - Effect size
  - Event rate
- More complex logistics
- Sacrifices study power

Enrollment and Analyses

- EMR registry based enrollment
- Recruiting prevalent patients
- Internal validation methodology
- Data sharing and leveraging endpoints from prior completed trials and registry data
- Joint modeling (time to event and longitudinal data)
- Incorporating PROs

Endpoint Considerations

- Frequency
  - Duration of observation
  - Acuity of population
  - Relatively small population with relatively low rate of highly morbid events and mortality
- Variation in measurement and events
  - Uniform measurement and stable endpoints
- Surrogate directly related to both treatment and ideal endpoint

Subject Selection

- Tight criteria
  - –Reduces variability and sample size
  - –Excludes subjects at risk of treatment complications
  - –Includes subjects most likely to benefit
  - –May restrict to advance disease, compliant patients, etc.
  - –Slows enrollment
  - –"Best case" results
    - Compliant low-risk patients with ideal disease stage
    - High risk patients with strong likelihood for event (enriched trials)
- Loose criteria
  - –Increases variability and sample size
  - –Speeds enrollment
  - –Enhances generalizability
    - "Real world" participants

The Value of Composite Endpoints

- Typically to increase statistical power and limit resources necessary if a therapy is likely to have similar effects on endpoint components
- Incorporate multiple clinically relevant events which may be ignored with a single endpoint
- Reporting of individual components for prospective hypothesis generation
- Address multiple pathways of long term outcome (e.g. graft failure)
- Concern of competing risks with surrogate endpoint alone (ignoring more severe events)

Considering Weighted Composite Endpoints

- Benefit is to apply appropriate ‘value’ on given clinical event
- May increase power from ‘all-cause’ composite and reduce variation if treatment effects are in same direction
- Big question is often how to weight and does the weighting apply equally by therapy, population, etc.

Case example

- Two-arm superiority trial
- Traditional primary outcome measure of graft loss or death or BPAR

	Control Arm	Intervention
N	120	120
Primary Outcome	35% (42/120)	28% (33/120)
	p=0.21	
Individual components		
BPAR	5 (4%)	28 (23%)
Graft loss	27 (23%)	3 (3%)
Death	10 (8%)	2 (2%)

Case example

- Two-arm superiority trial
- Weighted composite endpoint results
  - Death = 1.5
  - Graft loss = 1.0
  - BPAR = 0.2

	Control	Intervention
N	120	120
Outcome (weighted endpoint)	∑x = 44 Var(x)=0.6	∑x = 11.8 Var(x)=0.29
	p=0.04	
Individual components		
BPAR	5 (4%)	28 (23%)
Graft loss	27 (23%)	3 (3%)
Death	10 (8%)	2 (2%)

Polling Question:
Why aren't we using more surrogate endpoints in transplant trials today?

1. There are no existing surrogates that have been developed that are good enough for use in clinical trials
2. There are numerous existing good surrogates and we have no consensus which is best
3. Regulatory bodies (e.g. FDA) are not receptive to new surrogate endpoints
4. There is no compelling need for use of new surrogate endpoints in transplantation

The biggest hurdle is using any weighted composite endpoint

Other endpoints..
- DSA
- Renal function
- NODM
- Proteinuria
- Biopsy grade

Etc. etc..

Conclusions

- There are numerous approaches to study design and analysis that may be under utilized in transplantation but address some of the challenges in our field for clinical trial development

- Perhaps the most important hurdle to advancing clinical trials and encouraging innovation and development is establishing new endpoints that are more sensitive to potential therapeutic effects