Towards Optimal Trial Design for Novel Endovascular Therapies for CLI

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Disclosures

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The Conundrum of “Benchmark” in CLI Population

- RCT represent ethical, economic, scientific, & practical challenges
- Insistence on RCT may slow pace of development or keep new technology out of reach for US pts
- Rapid pace of technology may make results of RCT obsolete

RCT remain the gold standard for adoption of new therapies, or any paradigm shift in disease management

Clinical Trials Factoids

- 90% of drugs that reach the clinical stage never make it to the FDA & commercialization
- 70% of phase-III drug trials fail
- Device landscape is not much better!


Clinical Trials Factoids

- Only half of the rejected drug applications are due to lack of efficacy¹
- It is crucial to invest the time and resources early in the design process to avoid unnecessary delays

¹http://www.pharmaceuticalnews.com/files/Clinical

Why Trials Fail?

- Lack of efficacy/safety
- Insufficient proof of concept data!
- Trial design inconsistent with clinical endpoint(s)
- Lack of enrollment/retention (pt recruitment is a team effort)
  - Difficult incl/excl criteria (rigorous entry criteria not needed in PRT)
  - Technology not exciting; lack of excitement of investigators/patients
  - PI not being a good champion of the trial
- Study under-funded
- Poor study execution
**Pre-Design Checklist**

- Understand the technology
- Understand the disease process
- Can the technology modify disease variables?
- What type of trial is needed to measure the treatment effect?
- What are the goals of the trial?
- Testing a therapeutic strategy that includes the technology or the technology itself?

**Failure Triggers**

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<tr>
<th>Drivers of failure</th>
<th>Examples</th>
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| Inadequate basic science | - Animal results not reproducible in humans  
- Poor understanding of the target disease |
| Flawed study design | - Wrong endpoint  
- Wrong I/E criteria  
- Patient selection bias  
- Insufficient sample size |
| Suboptimal drug dose or device type selection | |
| Flawed data collection & analysis | - Over-optimistic assumption  
- Missing data, attrition bias, wrong statistical tests |
| Study operation & execution | - Poor site & PI selection  
- Recruitment issues, poor enrollment, dropouts  
- Non-compliance  
- Missing data |
| Other | Insufficient assessment of landscape & current standards of care & precedents |

**Case of Poor Understanding of Mechanism of Action**

- Biologic therapies
  - Gene therapy (naked DNA, plasmid, vectors, etc)
  - Cell therapy (undifferentiated marrow, placental, adipose, etc)
  - Growth factors (HGF, VEGF, etc.)
- What is the optimal dose??
- What is the optimal route of delivery??
- Who is the optimal patient?
- What are measuring? Is that the right parameter??

**Case of Poor Understanding of Target Disease**

- Therapy X is well-studied in animal models
- Proof of concept established (BP, capillary density, arterial flow, angio score, etc. all measured & positive)
- Mechanism of action understood (somewhat): increased eNOS & VEGF expression

**DCB in BTK**

- IN.PACT DEEP
  - Likely due to suboptimal balloon platform & coating process
- Biolux
  - Small underpowered study
- Lutonix BTK showed a drug effect but …
Clinical outcome does not always tell the whole story in patients with CLI

**Improved Clinical Outcome is Multifactorial**
- Revascularization is necessary but not sufficient
- Multiple determinants of survival
- Multiple determinants of wound healing
- Multiple determinants of amputation
- Multiple determinants of success of revascularization

*In complex diseases progress is incremental.*

**Problems with Clinical Endpoints in CLI**

At 30 male with 3rd toe NHW, ulcer healed and pain resolved by 3 months

**Limitations of Clinical Endpoints in CLI**

- At 3 months, ATA lesion recurred but TPT stent patent – pt asx
- At 6 months, ATA occluded, wound recurred *BUT* TPT stent widely patent
- In a trial only measuring clinical endpoints, DES would have failed despite the fact that it did what it was supposed to do!
• ATA lesion failed within 30-days but pt did well clinically

• In a trial evaluating "clinical success" only, this patient would count as "success" despite the failure of atherectomy!

### Optimal time to measure an effect

<table>
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<tr>
<th>Time</th>
<th>Outcome</th>
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### Optimal patient population

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Minimal dz burden</th>
<th>Severe dz burden</th>
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<tbody>
<tr>
<td></td>
<td>Therapy A</td>
<td>Therapy B</td>
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</table>

### Conclusion

• Technology needs thorough preclinical evaluation
• Study design & execution should be vetted thoroughly
• Study endpoints should be clinically relevant & based on objectives of treatment but ...

For better understanding of the incremental contribution of a new technology or treatment strategy in CLI, adoption of surrogate endpoints is necessary.