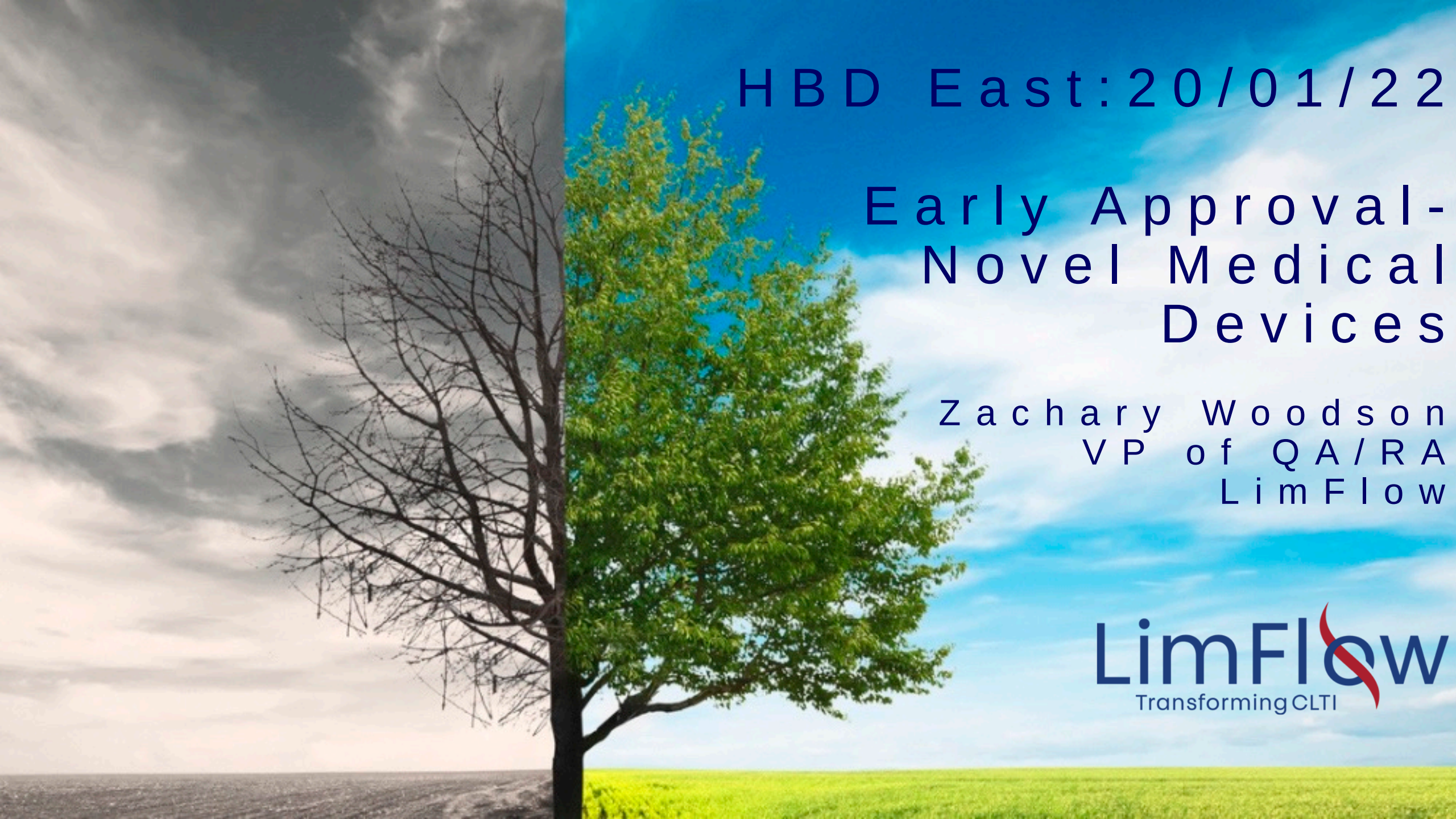

HBD East: 20/01/22

Early Approval- Novel Medical Devices

Zachary Woodson
VP of QA/RA
LimFlow

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Background

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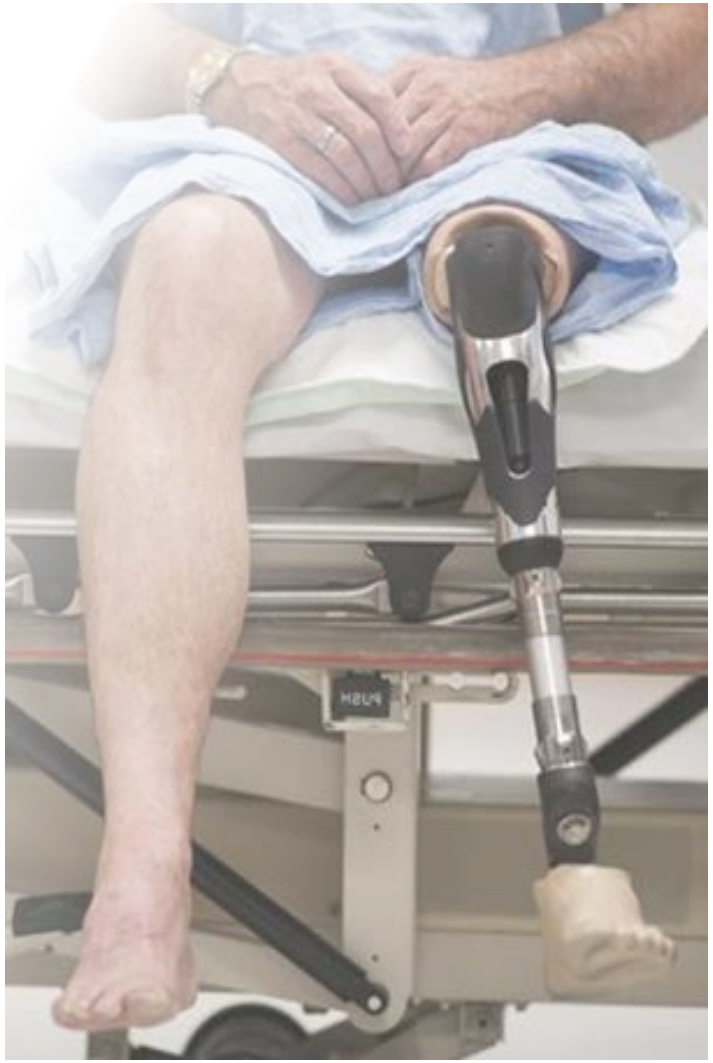
LimFlow Focus – Limb Salvage for CLTI Patients



Every
2 MINUTES,
a leg is lost to
ischemia-related amputation in US&EU

19 average hospital admissions per year

$800k in per patient direct healthcare cost

Up to **10%** **die before discharge**

Up to **60%** **die at 1 year**

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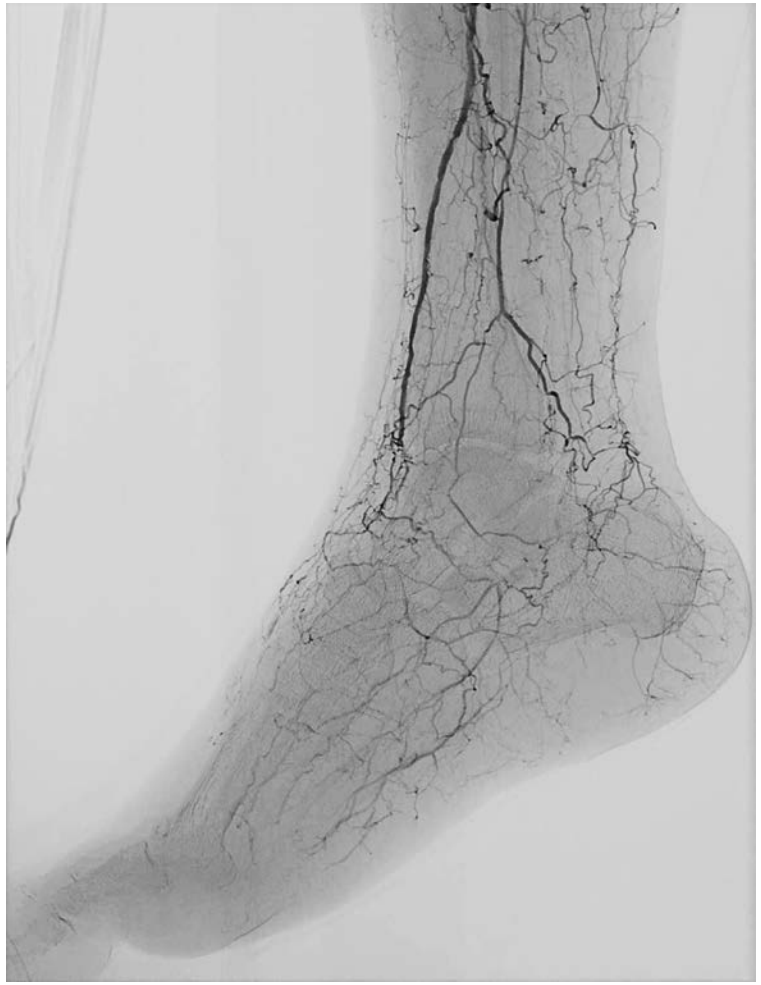
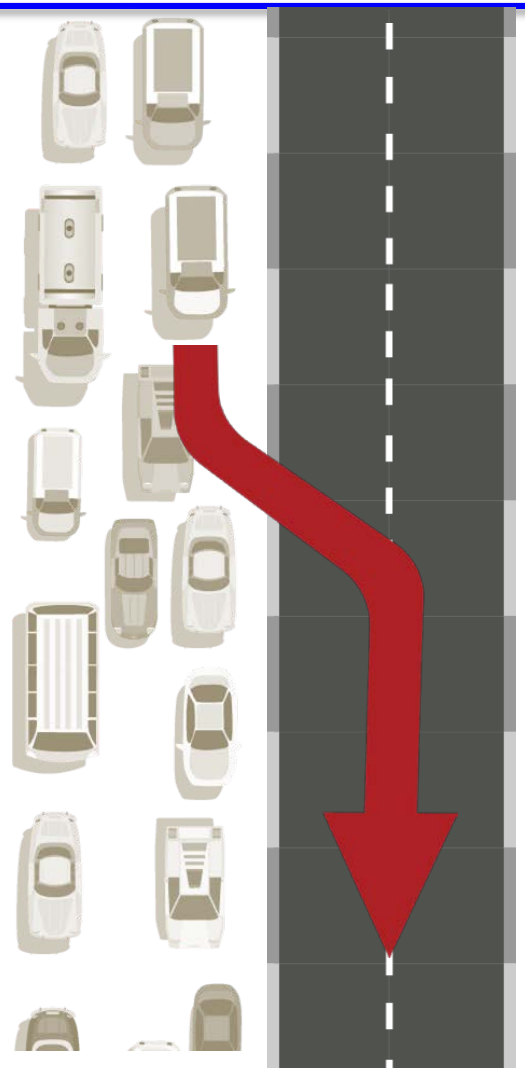
Why Current Therapies Fail

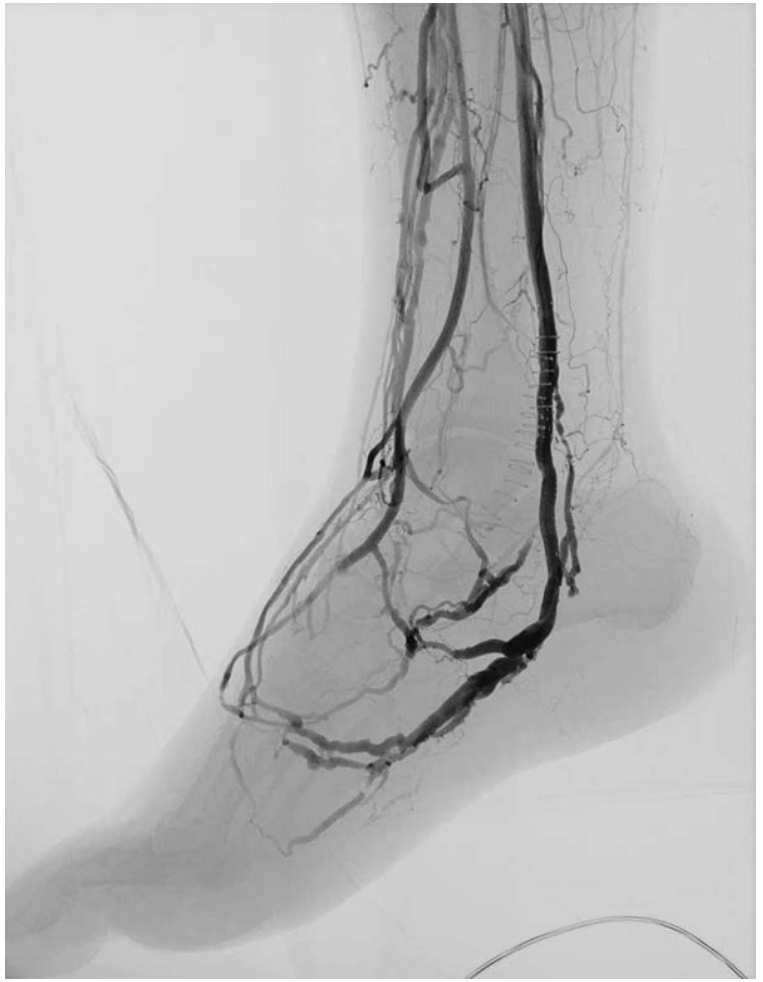
The distribution system within the foot of many CLTI patient is irreparably damaged

- High prevalence of medial artery calcification and small artery disease
- Significant comorbidities (Diabetes mellitus / end stage renal disease)
- Presence of a wound changes perfusion requirements
- Flow to ankle ≠ wound healing

Deep Venous Arterialization –
Alternative Perfusion Pathway







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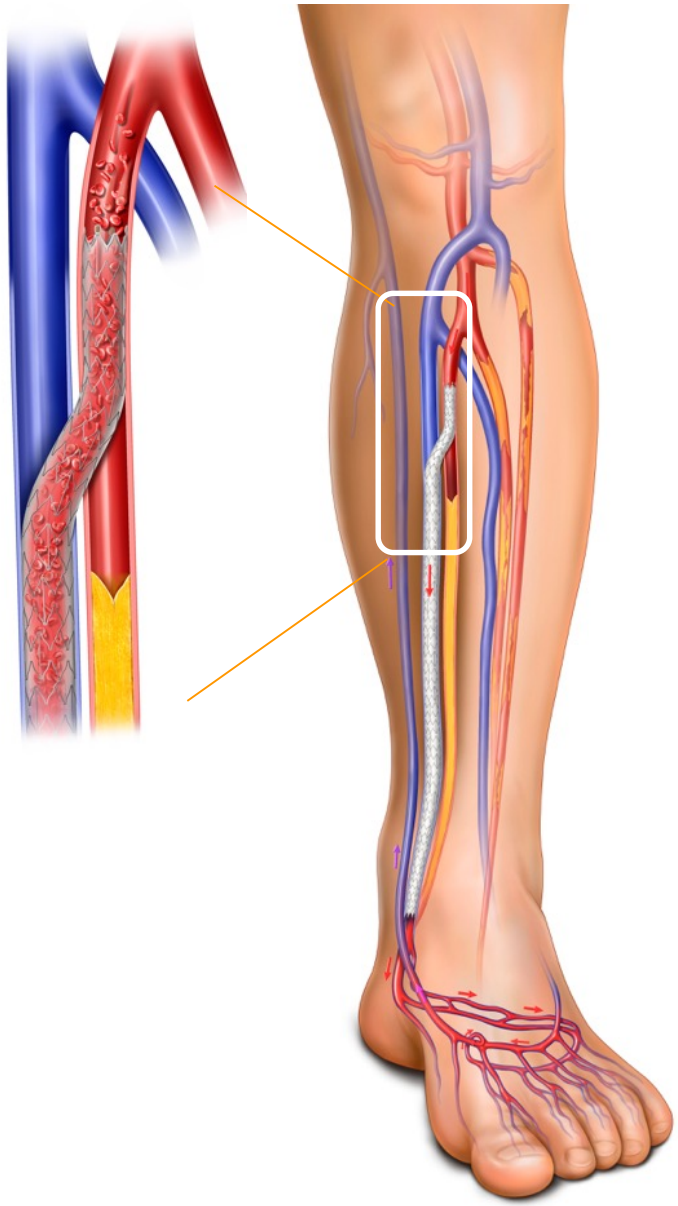
LimFlow pDVA

- Leverage healthier veins as a conduit
- Create new routes to perfuse tissue



Arterio-venous crossing

Catheters

Vein preparation

Valvulotome

Flow focalization

Conical & Straight Stent Grafts

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Novel Therapy Challenges

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Population

Large unmet need in patients with no surgical or endovascular treatment options

Challenge to identify / characterize a rarely studied population

- High rate of comorbidities
- Target population often excluded from traditional device studies
- Professional Society guidelines not widely understood (Wifi) or influenced by age or specialty (Rutherford)
- Support from Key Opinion Leaders crucial

Study Design

RCT vs Single-Arm

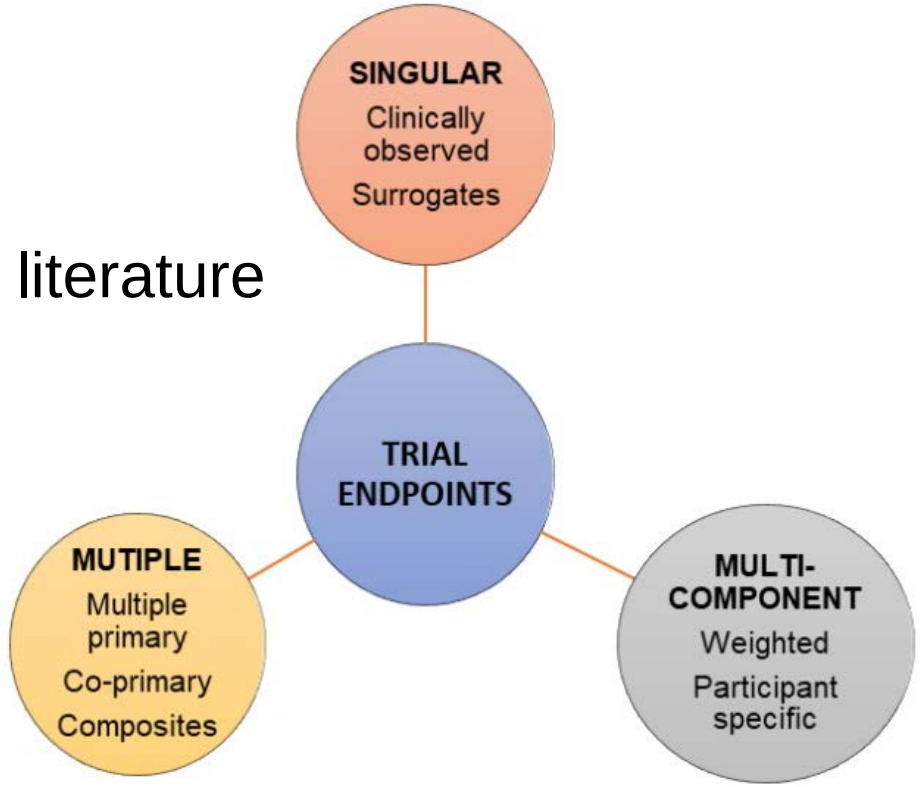
- Ethical challenges in a “no option” population
- Performance Goal – challenge to establish with literature

Statistical Approaches

- Frequentist
- Bayesian - adaptive

Clinical endpoint vs Surrogate

- Amputation Free Survival vs Patency (historically used for stents)



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Inclusion / Exclusion

Establishing which criteria are important for a population that is rarely studied

- Definition of “no option” the most contentious topic with FDA (surgical options) & PMDA (interventional options)

Accounting for potential geographical considerations

- Dialysis patients typically excluded from PAD studies
- Target population in Japan almost universally on dialysis
- The typical Japanese dialysis patient has a much greater life expectancy
- I/E used to identify US dialysis patients that mimic Japan

Regulator Interaction

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Pre-Submissions: Valuable Tool

Early Communication

- Take advantage of the pre-submission process to maximize early communication, may need to help educate FDA personnel
- LimFlow needed several pre-submissions due to the complexity of our system (4 devices) and the uniqueness of our therapy
- Multiple pre-submissions to review in vivo, in vitro, biocompatibility, etc. testing strategies
- Even with multiple meetings there can still be challenges in key areas like animal testing, biocompatibility, and study design

Breakthrough Device Program

- Great program for new technologies, facilitates greater communication with FDA
- Very helpful to small companies, like LimFlow
- Beneficial in addressing some aspects of reimbursement with future payors
- Highly recommended if your technology qualifies

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Early Feasibility Studies

Europe is no longer the preferred option for early clinical work

- New Medical Device Regulations (MDR) and MEDDEV guidance make clinical work in the EU very burdensome

FDA has done a great job addressing physician and industry feedback

- EFS viewed by many start-ups as the preferred pathway to collect early clinical evidence
- Verification and validation requirements remain, but in general FDA has been reasonable regarding data needs to initiate an EFS
- Allows for early data collection to help define pivotal study, but try to size appropriately so you can move quickly to pivotal

Harmonization by Doing – Lessons Learned

Great option to allow for potential entry into Japan without doing a stand-alone study or relying solely on foreign data

Key learnings:

- Like FDA, interact with PMDA as much as possible, LimFlow was quite far along with our FDA interactions before considering Japan
- Support from physicians in Japan to help champion your therapy is important, they can also help identify potential population differences that could impact your study design
- FDA is available to support, should it be needed
- Find a good in-country CRO and do not underestimate translation costs and timing
- The FDA/PMDA testing requirements are not identical (both agencies have been flexible in deferring some testing to a commercial application)

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Current Challenges

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COVID-19

The impact of COVID-19 on clinical study outcomes is not yet known

The impact of COVID-19 on study enrollment is clear

- Some hospitals stop/pause studies due to being overwhelmed with COVID patients or have a lack of staffing to support trials

Consultation meetings performed remotely

- Challenge to hold such important meetings via teleconference considering translation needs, time zone differences, etc.

Travel Restrictions

- Inability to travel and support cases


Thank you!
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