The Regulatory Imperative
The impact on practice of lung transplantation

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CUTTING EDGE of TRANSPLANTATION

TRANSPLANT SUMMIT 2018
Breaking Through Regulatory Barriers to Unleash Transplant Innovation

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The Regulatory Imperative -
Impact on practice of lung transplantation.

I have no conflicts of interest to declare
Goals:

1: discuss the *regulatory imperative* in lung transplantation (LTx)

2: review current regulation *in this setting*

3: describe the *impact* on clinical practice
IT'S A GREAT INVENTION, BUT WHAT IF IT FALLS INTO THE WRONG HANDS?
Evolution of Lung Transplantation

• 1960’s  Experimental Phase
  - First human lung transplant

• 1980’s  Clinical Implementation Phase
  - H/L first
  - 83: Single
  - 86: BSLTx

• 2000…  Wider Application Phase
  - Program Growth
  - Clinical Refinements
  - Performance markers

http://www.jhltonline.org/article/S1053-2498(14)01181-4/fulltext
Weill et al ISHLT Consensus document JHLT 2015;34: 1-15
https://www.ted.com/talks/charity_tilleman singing after a double lung transplant
Evolution of Lung Transplantation

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- **Present** Regulatory Phase?
  - Post LAS
  - Recipient challenges
  - Outcome Limitations
  - Restrictive Policies

https://www.ted.com/talks/charity_tilleman_singing_after_a_double_lung_transplant
Maxwell BG et al; Impact of Lung Allocation Score on Survival Beyond 1 Year; AJT 2014;14:2288pp
Klesney-Tait J et al ; Starting a Lung Transplant Program. Chest 2015; 147(5); 1435pp
IT'S A GREAT INTERVENTION
BUT WHAT IF IT FALLS INTO
THE WRONG HANDS?
Regulation

“...any government measure or intervention that seeks to change the behaviour of individuals or groups”

A) Maintaining patients’ rights and public’s interests &
B) Monitoring / restricting practitioners’ and programs’ behaviors

www.brtf.gov.uk Better Regulation Task Force; Principles of Good Regulation
Regulation

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www.brtf.gov.uk Better Regulation Task Force; Principles of Good Regulation
“Practice” of Regulation

- do nothing
- campaign and educate
- use the markets
- introduce financial incentives

‘let’s just have a code of d’honor’

www.brtf.gov.uk Better Regulation Task Force; Principles of Good Regulation
“Practice” of Regulation

- do nothing
- *(campaign and educate)*
- *(use the markets)*
- introduce financial incentives
  1) provide self-regulation and voluntary codes
  2) introduce prescriptive regulation

www.brtf.gov.uk  Better Regulation Task Force; Principles of Good Regulation
Regulation Principles

Proportionality
Accountability
Consistency
Transparency
Targeting

[www.brtf.gov.uk](http://www.brtf.gov.uk) Better Regulation Task Force; Principles of Good Regulation
Shining a light – Safer Healthcare through transparency, NPSF National Patient Safety Foundation’s Executive Summary
Regulation Policies *should*...

1. identify accountability
2. be enforceable
3. be easy to understand
4. have broad public support
5. be balanced and avoid knee-jerk reactions
6. reconcile contradictory policy objectives
7. balance risks, costs and benefits
8. avoid unintended consequences
9. be relevant to current conditions
The Practice of Lung Transplantation

Patients / Public
- Particular Utility
- Demanding Endeavor
- Expectations
- Risks v Benefits

Practitioners / Programs
- Specialty Service
- Complex Process
- Scope of practice
- Privilege
- Prudence
Healthcare Industry Regulation in US

- The Anti-kickback Law.
- The False Claims Act.

- Patient Protection and Affordable Care Act.
- Health Information Technology for Economic & Clinical Health (HITECH) Act.
- HIPAA.
- Physician Payments Sunshine Act:
  - Drug Regulations
  - Employment and Labor Regulations
  - Hazards and Waste Removal Regulations

https://www.cms.gov/index.html
Transplant Healthcare Regulation in US

• The Stark Law: self-referral regulations.
• The Anti-kickback Law.
• The False Claims Act.

• Patient Protection and Affordable Care Act.
• Health Information Technology for Economic & Clinical Health (HITECH) Act.
• HIPAA.
• Physician Payments Sunshine Act:

• Drug Regulations
• Employment and Labor Regulations
• Hazards and Waste Removal Regulations

• Final Rule (DHHS)
• Social Security Act
• CLIA Law (Labs & CDC)
• Certification Rules & Process (42 Code Fed Regs)
• Program responsibilities, Safety & Oversight Compliance

https://www.cms.gov/index.html
https://www.cdc.gov/clia/
Regulatory Drivers & metrics

- Information, Processes, Culture
- **Metrics**: plan-do-check-act +repeat

- Risk Analysis
- Security Controls
- Best Practice Frameworks

- Certification Standards
- Compliance Status
- Audit Cycles

- Vulnerability & Threats (Internal v External)
- Performance targets v clinical outcomes

- Admin (Internal); Technical (Logical); Physical (Hardware)
- Processes; Service Guidance; Organizational Structure (COBIT5)

- Enablers (Policies, Governance)
- Ongoing Alignment
Program Administration in LTx

Practice management
Transplant volume
Recipient outcomes
Quality measures

Financial status*
Institutional support*

- Failure rate of new programs is > 40%
- Resource provision
- Program strategy
- Viability threats
Examples of the regulatory imperative

1. identify accountability
2. be enforceable
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“was it allocated or complicated?”
Regulatory Imperative in LTx:
Example 1: Organ Allocation

- UNOS / OPTN
- policies
- procedures
- SRTR data

- Operational complexity
- Analytical capacity
- Impact of latency
Example 1: Allograft Allocation

- LAS principles
- Post LAS implementation
- LAS v Outcomes
- Geographic Challenges

Goal is to ensure EQUITY

1. Proportionality
2. Accountability
3. Consistency
4. Transparency
5. Targeting

Example 1:
LAS role in the Regulatory Imperative

- Reduced wait times
- Improved equity
- Efficient placement
- Increased Utilization
- Higher Acuity

- Policy application via DSA
- Not immune to external forces
- ‘Forced’ Policy Modification

Currently:
- Litigation > Federal Directives >
  UNOS Policy change > OPO & practice
  pattern impact

*Did not “avoid unintended consequences”*


Example 2: Regulatory Imperative in LTx

Survival metrics

- SRTR database
- Registry support
- Public information
- Enables CMS quality assurance surveillance

- Program specific
- Comparative quality
- Improvement options

- W/List parameters
- Graft Function stats
- 1 Survival metric

- May impact transplant rate
- Data could be stratified
- CUSUM analysis feasible

Grigg; F; et al. (2003). "The Use of Risk-Adjusted CUSUM and RSPRT Charts for Monitoring in Medical Contexts". Statistical Methods in Medical Research. 12 (2): 147–170
Example 2: Regulatory Imperative in LTx
Survival metrics / refinements

- **LAS based** W/List parameters
- **PGF adjusted** Graft Function stats
- **Weighted 1** Survival data

*Figure 2*: CUSUM chart monitoring complications. In 2009 the expected risk is 7% (dotted line) per patient. In 2009 there is an upwards slope in 2010 the slope increases however there is some decrease of the curve around case 1000. The full line in 2010 shows the CUSUM curve for an expected risk of 5% for a complication.
Example 2: Regulatory Imperative in LTx
potential consequences of current metrics

- CMS “generics”
- CMS LTx mandate
- CMS monitoring

- Certification Issues
- Insurance recognition
- Viability of Program

- A “need for mitigating factors that could justify inferior outcomes under specific circumstances”.
- “Failure to reach consensus on such a mechanism for appeal may result in risk-averse behavior by transplant centers with respect to innovation and therefore hamper the ability to advance the field of transplantation.

- Additionally general risk-adverse strategy in lung transplantation
  - ECMO candidates
  - Pulmonary Hypertension Candidates
  - Re-do Lung Transplant Candidates
  - Advanced Age Candidates
  - Avoidance of ECD Allografts

Example 3: The Regulatory Imperative Impact on Program Growth

- Wait List issues
- Referral paradox
- Transplant Rate
- Low volume predicament

The Regulatory Imperative and LTx Program Growth

“reconcile contradictory policy objectives”
The Regulatory Imperative and LTx Program Growth

“balance risks, costs and benefits”
The Regulatory Imperative and LTx Program Growth

- Strategic Demands
- Regulatory Realities
Example 3: Regulatory Imperatives in LTx
Device Regulation: ECMO in LTx

distinct Indications for “Bridging” in LTx

1. **Bridge to Native Lung Injury Recovery**
   (Reversible etiology of Respiratory failure)

2. **Bridge to Lung Transplantation**
   (Candidates listed with Endstage Respiratory failure)

3. **Recovery after Primary Graft Dysfunction**
   (Acute reperfusion related lung injury)

*not factored in 1 Y survival metrics - might need to be recognized as mitigating in some circumstances*

Support Therapy for Lung Failure: The utility of device therapy; C Wigfield et S Srinathan
Difficult Decisions in Surgery: An Evidence Based Approach; 2014 Ed M Ferguson
ECMO as “Bridge” to Lung Transplantation

Mechanical bridges to transplant

ECLS recommended:
- Young age.
- Absence of multiple-organ dysfunction.
- Good potential for rehabilitation.

ECLS not recommended:
- Septic shock.
- Multi-organ dysfunction.
- Severe arterial occlusive disease.
- Heparin-induced thrombocytopenia.
- Prior prolonged mechanical ventilation.
- Advanced age.
- Obesity.

Is existing regulation “still relevant to current conditions”?

de Perrot M et al. The Journal of Heart and Lung Transplantation, Vol 34, No 1, January 2015
IT'S A GREAT INNOVATION
BUT WHAT IF IT FALLS INTO THE WRONG HANDS?
Example 4: Regulatory Imperative in LTx
Impact on innovation & progress

- FDA is challenging
- FDA has jurisdiction claims Re therapeutics
- Task mastering
- Timeliness
- Transparency

- Diffusion of Innovations*
- Technology development in complex systems
- EVLP Trial dimensions
- DCD Practice in US
- Evidence processing
- Outcome impact

Example 4: Device Regulation
Ex Vivo Lung Perfusion trials

• HELP trial data
• Solution is a ‘device’
• NOVEL design
• PMA NOVEL extension experience

• EBM v best evidence available
• Data replication
• HDE confounder
• Doomed by delay
• Financial facts

Sanchez P G The NOVEL Lung Trial One-Year Outcomes 2014 Vol 33(4,) Supp, S71–S72
Abecassis M M et al American Socity of Transplant Surgeons Transplant Center Outcomes Requirements – A threat to Innovation AJT 2009; 1279pp
Regulatory Imperative in LTx:
what’s the Impact on practice?

- Risk Aversion
- Compliance Coding
- Personnel needs
- Stifled Innovation
- Cost Conundrum

Is existing regulation “still relevant to current conditions”?

Darrow JJ et al; The Regulatory Accountability Act 2017 - Implications for FDA Regulations and Public Health NEJM 2018; 378: 412 pp
The “Imperative”

– essential to monitor
– underlying motif
– urgent to revise

• Ensure compliance
• Remain operational
• Promote practice

Refine (but not to add to) current metrics
Limitations to Lung Transplantation

- **Suitable Lung Donor Shortage**
- DDND maxed at 9000
- SCD now smaller proportion
- OPO’s Frustrations
- Mortality on W/L up to 30%
- PGD still at 20%
- BOS remains longterm issue

- W/L deaths adjusted
- Conversion Rate endpoint
- PGD 3 Incidence
- LAS weighted CUSUM plots
- 1 year survival adjudication

*Is existing regulation “still relevant to current conditions” ?*

Botha et al Extended Criteria in Lung Transplantation: Impact on Organ Allocation
http://www.jtcvsonline.org/article/S0022-5223(06)00097-3/abstract
Maxwell BG et at; Impact of Lung Allocation Score on Survival Beyond 1 Year; AJT 2014;14:2288pp
Future Regulatory Issues in LTx

- Broader allograft sharing
- Donor DSA v Geography
- Donor management
- Tissue engineering
- Genetic modification
- Device development

‘bioreactor’ lungs off the shelf:
CMS

SRTR

UNOS / OPTN

CDC

DHS

HRSA

CMS

SRTR

UNOS / OPTN

CDC

DHS

HRSA

Private Payers
HC Networks

OPO

FDA

Foundations
Economists
Ethics Committee

Program / Public representation
‘The Regulatory Accountability Act 2017’:  

Risk: Regulatory paralysis  
Risk: Loss of current “certainties”  

• possible paradoxical effects.  
• challenge to scientific standards.  
• lobby interest will have a role.  

1. questions accountability  
2. What’s enforceable?  

Darrow JJ et al; The Regulatory Accountability Act 2017 - Implications for FDA Regulations and Public Health NEJM 2018; 378: 412 pp
Conclusions

• Complexity of “Regulatory Imperatives” in LTx are due to *practicalities* (beyond the regulatory principles).

• Associated burden can be reduced with improved *relevance* of “metrics” (more accurately assess program performance).

• Innovation should be supported and *dialogue* between stakeholders and agencies is needed.