Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Transforming emphysema treatment: first-in-man to clinical commissioning of Bronchoscopic Lung Volume Reduction.

Period when the underpinning research was undertaken: 2000 - 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Nicholas Hopkinson	Reader in Respiratory Medicine	2001 – 2004 2006 to date
Pallav Shah	Professor of Respiratory Medicine (Honorary)	1999 - present
Duncan Geddes	Professor of Respiratory Medicine (Honorary)	1978 - present

Period when the claimed impact occurred: 2015 - 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum 100 words)

Imperial College researchers have taken bronchoscopic lung volume reduction techniques for people with severe emphysema from proof-of-concept, through first-in-man case series and randomised controlled trials demonstrating clinically significant improvements in lung function, breathlessness, exercise capacity, quality of life and survival, to an established place in both NICE and international guidelines for COPD management. The team established a national register and identified inequalities of access, which, combined with evidence of effectiveness and value, led to approval for Specialist Commissioning by NHS England in November 2020, allowing treatment for thousands of breathless and disabled COPD patients with otherwise irreversible disease.

2. Underpinning research (indicative maximum 500 words)

There are 1,300,000 people with a diagnosis of chronic obstructive pulmonary disease (COPD) in the UK. In selected patients with lung hyperinflation due to emphysema, surgical removal of the worst affected area of lung reduces gas trapping and allows the relatively healthy areas of lung to function more effectively. Around 1% of COPD patients are suitable to benefit from this technique. Lung volume surgery involves resecting target lung – it is effective, but little used because of concerns over morbidity and cost.

Researchers at Imperial College London have demonstrated the clinical effectiveness of an alternative approach, bronchoscopic lung volume reduction, as a treatment for emphysema through case series, physiological studies and definitive randomised controlled trials.

Bronchoscopic lung volume reduction is achieved by placing endobronchial valves into the airways supplying the target lobe of lung. These allow air to leave but not enter, causing the target lobe to collapse and facilitating safe lung volume reduction. The approach is less invasive than surgery and can be more widely applied with less risk of morbidity and mortality with a reduction in usage of healthcare resources.

The Imperial College team conducted the first randomised controlled trial (RCT) of lung volume reduction surgery (LVRS) which proved the concept that lung volume reduction for people with emphysema improved breathlessness, quality of life and exercise capacity (1). The researchers then demonstrated, in the first case series describing the use of endobronchial valves for lung volume reduction, that they could be placed safely and that the procedure improved lung function (2).

Further work in clarifying the importance of achieving lobar occlusion demonstrated that endobronchial valves reduced dynamic hyperinflation during exercise and that this was associated with a substantial improvement in exercise capacity, particularly in individuals where radiological atelectasis (where the target area of lung collapses down) was demonstrated (3). The team established the importance of careful patient selection - if emphysema has broken down the barriers between lobes, collateral ventilation occurs, and valve placement is ineffective because air can still get into the target lobe from adjacent lung.

The team of researchers also demonstrated a survival benefit with successful valve placement (4), which is important given the absence of treatments that alter the natural history of COPD. They also established the beneficial impact of lung volume reduction (a) in improving oxygen kinetics because lung hyperinflation impedes cardiac function and (b) on ventilatory synchrony, using the novel, non-invasive optoelectronic plethysmography technique.

The Imperial College team went on to perform the first double-blind BeLieVeR-HIFi RCT of valve placement, funded by the NIHR-MRC EME programme (5), and to lead the TRANSFORM multicentre RCT (6). These studies confirmed clinically significant benefits in quality of life, breathlessness, lung function and exercise capacity.

The work of these researchers within the field of advanced therapies for emphysema have also demonstrated that LVRS can be conducted more safely in modern practice and that access to lung volume reduction techniques is highly inequitable, underling the importance of the decision of NHS England (NHSE) to support specialist commissioning.

3. References to the research (indicative maximum of six references)

(1) Geddes, D., Davies, M., Koyama, H., Hansell, D., Pastorino, U., Pepper, J., Agent, P., Cullinan, P., MacNeill, S.J., & Goldstraw, P. (2000). Effect of lung-volume-reduction surgery in patients with severe emphysema. *New England Journal of Medicine*; 343(4): 239-245. DOI.

(2) Toma, T.P., Hopkinson, N.S., Hillier, J., Hansell, D.M., Morgan, C., Goldstraw, P.G., Polkey, M.I. & Geddes, D.M. (2003). Bronchoscopic volume reduction with valve implants in patients with severe emphysema. *Lancet;* 361(9361): 931-933. DOI.

(3) Hopkinson, N.S., Toma, T.P., Hansell, D.M., Goldstraw, P., Moxham, J., Geddes, D.M., & Polkey, M.I. (2005). Effect of bronchoscopic lung volume reduction on dynamic hyperinflation and exercise in emphysema. *Am J Respir Crit Care Med*, 171(5): 453-460. DOI

(4) Hopkinson, N.S., Kemp, S.V., Toma, T.P., Hansell, D.M., Geddes, D.M., Shah, P.L., & Polkey, M.I. (2011). Atelectasis and survival after bronchoscopic lung volume reduction for COPD. *European Respiratory Journal*; 37(6): 1346-1351. DOI.

(5) Davey, C., Zoumot, Z., Jordan, S., McNulty, W.H., Carr, D.H., Hind, M.D., Hansell, D.M., Rubens, M.B., Banya, W., Polkey, M.I., Shah, P.L., & Hopkinson, N.S. (2015). Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomised controlled trial. *Lancet*; 386(9998): 1066-1073. DOI.

(6) Kemp, S.V., Slebos, D.J., Kirk, A., Kornaszewska, M., Carron, K., Ek, L., Broman, G., Hillerdal, G., Mal, H., Pison, C., Briault, A., Downer, N., Darwiche, K., Rao, J., Hubner, R.H., Ruwwe-Glosenkamp, C., Trosini-Desert, V., Eberhardt, R., Herth, F.J., Derom, E., Malfait, T.,

Shah, P.L., Garner, J.L., Ten Hacken, N.H., Fallouh, H., Leroy, S., Marquette, C.H., & Transform Study Team. (2017). A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (TRANSFORM), *Am J Respir Crit Care Med*; 196: 1535-43. DOI.

4. Details of the impact (indicative maximum 750 words)

COPD, the third leading cause of death globally after cardiovascular disease and cancer is a combination of chronic bronchitis and emphysema. In emphysema, the alveolar walls and small airways are destroyed, causing the lung tissue to become baggy and trap air. This gas trapping increases the work of breathing, restricts vital capacity and cardiac function and manifests as disabling breathlessness, impaired ability to do physical activity, reduced capacity to withstand acute exacerbations of the condition and premature death. Inhaled medication can relieve symptoms but does not alter the natural history of the disease and lung hyperinflation has been an intractable problem.

There are an estimated 16,000 people in the UK and 660,000 in Europe, who might be eligible for a lung volume reduction procedure, equating to approximately 1% of people with COPD. These procedures, indicated in patients with severe COPD who are highly symptomatic, improve breathlessness, exercise capacity and quality of life, as well as prolonging survival in a condition that is otherwise progressive and relentless. The scale of benefit with lung volume reduction is dramatic and typically far exceeds those seen with inhaled medications.

Initial case series investigations by the Imperial team generated a body of work on the physiological mechanisms and data on mortality benefit from successful valve placement - previously the only other interventions shown to improve survival in COPD were smoking cessation and supplemental oxygen in individuals with respiratory failure.

This led to funding of the BeLieVeR-HIFi trial, the first device study supported by the NIHR-MRC EME programme. The results of this RCT and the individual patient meta-analysis performed by the Imperial team, combined with data from the Dutch STELVIO trial, informed a Cochrane review [**A**]. Importantly the improvements in quality of life seen were double that observed with inhaled medication. Collectively this formed the evidence base on which the National Institute for Health and Care Excellence (NICE) health technology appraisal [IPG600] approved the use of endobronchial valve placement within the NHS in 2017 [**B**]. These data also informed international guidelines and clinical practice, with their inclusion in the international GOLD COPD guidelines.

These data, together with that from the Imperial-led multi-centre TRANSFORM trial contributed to the NICE COPD guideline committee making a clear recommendation that endobronchial valve therapy should be offered to appropriately selected patients in 2018 (NG115 recommendation 1.2.88) [**C**]. The decision was supported by data estimating the cost per quality-adjusted life years of endobronchial valve placement at approximately £22,500, putting it within an acceptable range for NICE [**D**].

This evidence of efficacy together with data gathered on inequity of access to the procedures led NHSE to approve endobronchial valve placement for Specialist Commissioning (November 2020) so that all patients within the NHS who are suitable should be able to access it [**E**].

Data from the UKLVR registry show that our work has led to 14 centres performing LVR procedures in the UK with around 500 lung volume reduction procedures performed since 2017. The Specialist Commissioning with associated funding and support for referral pathways, will lead to a substantial further increase in patient access and benefit.

Endobronchial valve placement is also now recognised in international guidelines for the management of COPD (e.g. the GOLD guidelines 2020, p63, “endobronchial valve placement

shows comparable benefits to LVRS but with fewer complications"), meaning that the impact has been global [**F**]. According to the website of one valve manufacturer >19,000 emphysema patients worldwide have already undergone an endobronchial valve placement procedure using their product [**G**]. Another manufacturer, Olympus, estimates that globally over 11,000 patients have been treated using their valve product [**H**].

The UK Taskforce for Lung Health states that lung volume reduction procedures remain an underused therapy. Newer and less invasive lung volume reduction technologies, such as valves, broaden the pool of eligible people to as many as 16,300 people in England who could benefit from such a procedure [**I**].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[**A**] Bronchoscopic lung volume reduction procedures for moderate to severe chronic obstructive pulmonary disease, van Agteren JEM, Hnin K, Grosser D, Carson KV, Smith BJ. Cochrane Airways Group: 2017. DOI. https://www.cochrane.org/CD012158/AIRWAYS_bronchoscopic-lung-volume-reduction-procedures-moderate-severe-chronic-obstructive-pulmonary-disease

[**B**] Endobronchial valve insertion to reduce lung volume in emphysema. Interventional procedures guidance [IPG600] Published date: 20 December 2017 https://www.nice.org.uk/guidance/ipg600. Archived here.

[**C**] Chronic obstructive pulmonary disease in over 16s: diagnosis and management. NICE guideline [NG115] Published date: 05 December 2018 Last updated: 26 July 2019 https://www.nice.org.uk/guidance/ng115. Archived here.

[**D**] Cost-Effectiveness of Endobronchial Valve Therapy for Severe Emphysema: A Model-Based Projection Based on the VENT Study. Pietzsch J.B. · Garner A. · Herth F.J.F. Respiration 2014;88:389-398 https://doi.org/10.1159/000368088

[**E**] NHS England Specialist Commissioning guidance: Lung volume reduction by surgery or endobronchial valve for severe emphysema in adults. Nov 2020 https://www.england.nhs.uk/publication/lung-volume-reduction-by-surgery-or-endobronchial-valve-for-severe-emphysema-in-adults/. Archived here.

[**F**] 2020 Global Strategy for Prevention, Diagnosis and Management of COPD https://goldcopd.org/gold-reports/ (page 94).

[**G**] Pulmonx Zephyr valve https://pulmonx.com/about-pulmonx/ (archived here).

[**H**] Confirmation of global patient numbers from Olympus (available upon request)

[**I**] UK Taskforce for Lung Health: A National Five Year Plan for Lung Health (Recommendation 3B P57) 2019 https://www.blf.org.uk/taskforce/plan. Archived here.