Institution: The University of Manchester		
Unit of Assessment: 2 (Public Health, Health Services and Primary Care)		
Title of case study: Definitive multinational efficacy trials and pioneering 'real-world' evidence informing treatments and international strategy for managing chronic obstructive pulmonary disease (COPD)		
Period when the underpinning research was undertaken: January 2008 – December 2017		
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:**
Jørgen Vestbo	Clinical Professor of Respiratory Medicine	2003 – present
Dave Singh	Clinical Professor of Respiratory Medicine	2003 – present
Ashley Woodcock	Clinical Professor of Respiratory Medicine	2000 – present
Period when the claimed impact occurred: January 2016 – December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Translational research at The University of Manchester (UoM) brought about a step change in the clinical management of COPD from simple inhaled therapies to more efficacious, safer novel combination inhaled therapies. Notably, Chiesi's Trimbow triple inhaler, approved by the European Medicines Agency (EMA) and available in 19 European countries, has simplified treatment for COPD patients. UoM research has informed Global Initiative for Chronic Obstructive Lung Disease (GOLD) international strategy and in 2019 was evidenced by the National Institute for Health and Care Excellence (NICE) in updating their COPD guidelines. The team initiated a paradigm shift for experimental medicine by evaluating 'real-world' effectiveness for the first time among primary care patients in a deprived population with high prevalence of smoking and co-morbid cardiovascular disease, a model that GlaxoSmithKline (GSK) now uses in trials in other diseases.

2. Underpinning research

Evidence for the effective clinical management of COPD is growing, but had been generated mostly from trials with highly selective inclusion criteria on the assumption that all patients respond similarly to efficacious treatments. Therapies, however, must work effectively for all affected patients who are treated in usual clinical practice. Research programmes led by **Vestbo**, **Singh** and **Woodcock** at the UoM filled this void in the evidence base. UoM conducted large multinational efficacy trials in patients with and without co-morbid cardiovascular disease (CVD), and carried out 'real-world' effectiveness evaluation in Salford - a city in Greater Manchester with a deprived, multi-morbid population.

Singh generated early evidence for the superiority of 'triple' therapy for patients with moderate-severe COPD [1]. In collaboration with Chiesi Farmaceutici (Parma, Italy), an inhaled corticosteroid and two long-acting drugs that dilate the airways (a beta-agonist and an anticholinergic) were combined in one inhaler, which is now marketed as Trimbow. The EMA had no prior experience with triple combination inhalers, so **Singh** and **Vestbo** designed the registration trials and conducted the efficacy trials leading to the first registration of a triple inhaler, six months prior to that of the closest competitor. To achieve this, UoM researchers conducted three large multinational double-blind randomised controlled trials (RCTs) in a mixture of primary, secondary and tertiary care sites as well as specialist investigation units: TRILOGY [2]; TRINITY [3]; TRIBUTE [4]. Conducted with 5,591 randomised patients in aggregate, these trials demonstrated conclusively that the new triple combination inhaler leads to therapeutic simplification and improved clinical outcomes, in

particular a significant reduction in exacerbations - a massive burden to patients and the main driver of costs in COPD.

With support from GSK, **Vestbo** designed and led the SUMMIT trial, which was the first large RCT of patients with COPD and CVD - the most common comorbidity in COPD, but an exclusion criterion in most efficacy trials. This vast experiment entailed randomisation of 16,590 patients at 1,368 centres in 43 countries - the largest trial of its type to be conducted. It showed no interaction between CVD and efficacy of inhaled medications and yielded reassuring patient safety data for this riskier patient population, leading to a better understanding of efficacy and safety of inhaled medications in patients with cardiovascular comorbidity [5]. **Woodcock** and **Vestbo** also designed and led the pioneering Salford Lung Studies (SLS) in collaboration with GSK. The studies showed an 8.4% reduction in moderate or severe exacerbations with fluticasone furoate-vilanterol therapy than with usual care but, critically, included patients with low socioeconomic status and a high prevalence of smoking and comorbidities and utilised routinely collected data in real-time for assessment of aspects regarding patient safety [6]. The two SLS 'real-world' effectiveness RCTs utilised electronic health records to examine treatment effects in COPD and asthma patients, respectively, as they presented to their GPs in usual clinical practice in a population with elevated prevalence of smoking and CVD. These studies thereby provided a representative evaluation of the effect of inhaled medication on exacerbations and their impact on pneumonia, a side effect of inhaled corticosteroids.

3. References to the research

1. **Singh D,** Brooks J, Hagan G, Chan A, O'Connor BJ. Superiority of "triple" therapy with salmeterol/fluticasone propionate and tiotropium bromide versus individual components in moderate to severe COPD. *Thorax* 2008; 63(7): 592-598. doi: 10.1136/thx.2007.087213 (144 citations, Scopus, 9 December 2020).

A randomised, double blind, double dummy, three-way crossover trial. Conducted at five centres in the UK and Belgium.

2. **Singh D**, Papi A, Corradi M, Pavlišová I, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, **Vestbo J**. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *The Lancet* 2016; 388(10048): 963-973. doi: 10.1016/S0140-6736(16)31354-X. (210 citations, Scopus, 9 December 2020).

The first one-year trial (of 1,368 patients randomised at 159 sites in 14 countries) comparing inhaled fixed triple therapy with a combination of an inhaled corticosteroid and a long-acting beta-agonist, showing superiority on lung function and exacerbation rate.

3. **Vestbo J**, Papi A, Corradi M, Blazhko V, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, **Singh D**. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomized controlled trial. *The Lancet* 2017; 389(10082): 1919-1929. doi: 10.1016/S0140-6736(17)30188-5. (187 citations, Scopus, 9 December 2020).

One-year trial (of 2,691 randomised patients at 224 sites in 15 countries) comparing inhaled fixed triple therapy with a long-acting anti-cholinergic, showing superiority on exacerbation rate, the primary outcome.

4. Papi A, **Vestbo J**, Fabbri L, Corradi M, Prunier H, Cohuet G, Guasconi A, Montagna I, Vezzoli S, Petruzzelli S, Scuri M, Roche N, **Singh D**. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *The Lancet* 2018; 391(10125): 1076-1084. doi: 10.1016/S0140-6736(18)30206-X. (198 citations, Scopus, 9 December 2020).

One-year trial (of 1,532 patients randomised at 187 sites in 17 countries) comparing an inhaled fixed triple therapy versus dual bronchodilator therapy, showing a reduced rate of moderate-to-severe exacerbations without raising pneumonia risk.

5. **Vestbo J**, Anderson JA, Brook RD, Calverley PMA, Celli BR, Crim C, Martinez F, Yates J, Newby DE, on behalf of the SUMMIT Investigators. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *The Lancet* 2016; 387(10030): 1817-1826. doi: 10.1016/S0140-6736(16)30069-1. (206 citations, Scopus, 9 December 2020).

The first large trial in COPD in which only patients with co-morbid CVD were included; CVD coexists in 30-40% of patients with COPD but is usually an exclusion criterion in efficacy trials. With 16,590 patients randomised at 1,368 centres in 43 countries, this remains the largest trial of its type published to date.

6. **Vestbo J**, Leather D, Diar Bakerly N, New J, Gibson JM, McCorkindale S, Collier S, Crawford J, Frith L, Harvey C, Svedsater H, **Woodcock A**, for the Salford Lung Study Investigators. Effectiveness of fluticasone furoate-vilanterol for COPD in clinical practice. *New England Journal of Medicine* 2016; 375(13): 1253-1260. doi: 10.1056/NEJMoa1608033. (107 citations, Scopus, 9 December 2020).

The first 'real-world' effectiveness trial in COPD comparing the initiation of a combination of inhaled fluticasone furoate and vilanterol with usual care. The study was entirely novel in its utilisation of local healthcare infrastructure and real-time electronic health records, with 2,799 patients randomised and almost 80 general practices and 130 pharmacies participating. It is the world's first trial of this type in any medical specialty.

4. Details of the impact

The contribution of COPD to the global burden of disease is substantial; in the UK alone, 1,200,000 people have been diagnosed. The incidence and prevalence of COPD is higher among deprived people and in poorer communities, and it is a salient driver of health inequality in the UK and in other countries. It is currently the third leading cause of death globally and almost 4,000,000 people diagnosed with COPD die each year worldwide.

Pathways to impact

Developing improved treatments with industrial partners

UoM have longstanding experience in running COPD efficacy trials and were approached by Chiesi Pharmaceutica to assist them in designing a streamlined trial programme for their fixed triple inhaler, Trimbow, and worked with GSK on the SLS.

Methodological advancement in experimental medicine

Traditionally, clinical trials were conducted as regular efficacy trials in highly selected patient populations with stringent diagnostic criteria, few comorbidities, and compliant participant behaviour. The UoM trials on COPD progressed from restricted efficacy trials to demonstrating efficacy in patients with relevant comorbidities [5] and to randomised effectiveness evaluation in usual clinical practice [6].

Committee membership

Vestbo has been a member of the Scientific Committee GOLD since 2006, and Singh since 2015. GOLD is an independent body, and its Strategy Document is the basis for many COPD guidelines, thereby providing advice in areas where guidelines do not exist.

Reach and Significance of the Impact

Simpler and more effective treatments for COPD patients

UoM worked with Chiesi to design a streamlined trial programme for their fixed triple inhaler, Trimbow, enabling this product to become the first fixed triple inhaler for COPD approved by EMA [Ai], based on TRILOGY and TRINITY (July 2017) [2,3]. EMA later expanded the label (March 2019) as a treatment for patients with moderate to severe COPD not adequately treated [Aii] based on TRIBUTE [4].

This fixed combination inhaler has led to therapeutic simplification and improved clinical outcomes. Chiesi explained, "*The possibility of taking all drugs needed by using only one inhaler considerably simplifies the treatment of patients, decreasing the burden on patients and may improve adherence*" [Aiii]. Improved adherence improves clinical outcomes, including exacerbations, which impair quality of life, lead to hospitalisation or death.

Commercial benefits

On working with UoM, Chiesi's Vice President stated, "*Chiesi R & D have benefitted enormously from this fruitful collaboration, and very much plan for it to continue to enrich our delivery of novel treatments for patients with high unmet medical needs"* [B]. In 2018 Trimbow generated sales of EUR40,000,000 and was commercially available in 19 European countries as at 31 December 2018 [C]. Following the label expansion based on TRIBUTE [4], Trimbow sales in 2019 totalled EUR127,000,000 [C].

Informing UK and international clinical management strategy

In July 2019, NICE recommended triple therapy as an option for some patients [D]. TRILOGY and TRIBUTE [2,4] were included clinical studies in the evidence review.

The GOLD Strategy Document, on which UoM researchers have had significant input, is the most referenced source document for the management of COPD worldwide. The GOLD global recommendations for COPD refer extensively to trials carried out in Manchester (including the six outputs that are listed in Section 2), with the triple combination trials (TRILOGY, TRINITY, TRIBUTE) referenced as *the* major evidence-base for triple therapy [E]. Before these conclusive multinational efficacy trials were conducted, there was no robust evidence supporting the use of this novel therapy. In a nine month period in 2019, the GOLD website recorded 337,711 hits from 211 countries (28,902 from the UK, second country after the US), the most recent GOLD Strategy document was downloaded 238,536 times, the teaching slide set 21,173 times, and the GOLD app has been downloaded 47,009 times [F]. GOLD's Executive Director confirmed, "*GOLD has relied on University of Manchester to contribute important research evidence on which our diagnosis and treatment recommendations are made*" [F].

From efficacy to 'real-world' effectiveness in clinical trials

The trials carried out by UoM [5, 6], represented a step change from regular efficacy trials to trials in clinical populations consisting of patients who will eventually receive the novel medications once registered and marketed. The 'real-world' SLS trial [6] documented effectiveness of a novel combination inhaler pre-registration, a world first, showing that early large-scale effectiveness trials are possible.

Eminent commentators in other medical specialities have commented that the SLS has shown the way in initiating a paradigm shift for effectiveness evaluation in experimental medicine and became an exemplar for obtaining 'real-world' evidence on effectiveness in a deprived population with many comorbidities early in the life cycle of a drug [G]. The SLS trial formed the basis of a National Institute for Health Research (NIHR) case study on delivering real world research in which they confirmed "*It demonstrates a major advance in the way we do clinical trials… There is an increasing demand for 'real world' methodology and data and the successful delivery of the Salford Lung Study has sparked interest across the commercial world"* [H].

GSK were UoM's industrial partner in SLS trials. At the National Academies of Science Engineering and Medicines Workshop in July 2018, GSK Senior Vice President confirmed the SLS trial had generated a reusable infrastructure and that lessons learned could be applied in other disease areas. GSK is now applying a similar model in cardiovascular and renal disease studies in the United States [I].

In 2020 EMA published their strategic goals and core recommendations in human medicine to 2025, committing to "*advancing patient-centred access to medicine in partnership with healthcare systems*" through the aim to "*promote use of high-quality real-world data (RWD)*

in decision-making" confirming the increasing importance placed on real world evidence in medical regulation [J].

5. Sources to corroborate the impact

A. Trimbow EC - regulatory approvals based on UoM research [2-4]:
   i. Chiesi press release 24 July 2017 – *confirms European (EMA) approval.*
   ii. Chiesi press release 6 March 2019 - *confirms expanded EMA authorisation.*
   iii. Chiesi press release 22 May 2017 - *confirms EMA's Committee for Medicinal Products for Human Use (CHMP)'s positive opinion.*

B. Letter of endorsement from Chiesi's Vice President and Director of R&D and Chiesi's Head of Corporate Drug Development, Chiesi (Parma, Italy), dated 16 January 2020. *Confirming the input and expert leadership from UoM in the studies leading to Trimbow's production.*

C. Chiesi Annual Reports 2018-2019 - *showing sales figures for Trimbow*. https://www.chiesipharma.se/en/annual-report-and-brochures/

D. UK NICE guideline NG115 Chronic obstructive pulmonary disease in over 16s: diagnosis and management. 5 December 2018 including Evidence Review I: Inhaled Triple Therapy July 2019. https://www.nice.org.uk/guidance/ng115 – *stating benefits of dual therapy and recommending triple therapy for some patients, citing UoM references 2 and 4 in clinical evidence review.*

E. GOLD - 'Global Strategy for Prevention, Diagnosis and Management of COPD (2020 Report)'. *The 2020 update cites numerous major published outputs that have been co-authored by UoM academics as well as all six of the outputs that are listed in Section 3 of this impact case study.*

F. Statement *confirming the importance of UoM work to GOLD from the Executive Director of GOLD and the GOLD Chair of Board of Directors, dated 8 September 2020.*

G. Articles referring to importance of SLS trial:
   i. Hemingway H, Asselbergs FW, Danesh J, et al. Big data from electronic health records for early and late translational cardiovascular research: challenges and potential. European Heart Journal. 2018;39(16):1481-1495.t al. *"… in cardiovascular disease there has not yet been a pragmatic phase III trial of a pre-license drug. The Salford Lung Study (GSK, relovair) is the world's first such trial and is set in a regional 'whole health system' EHR*." (p1491) - *demonstrates the ground-breaking nature of the SLS and its initiation of a profound paradigm shift across experimental medicine.*
   ii. Kalkman S, van Thiel GJMW, Grobbee DE, van Delden JJM. Pragmatic clinical trials: ethical imperatives and opportunities. *Drug Discovery Today*. 2018;23(12):1919-1921. *"By recruiting a large number of patients from a typical real-world setting, the SLS even managed to achieve a very high level of pragmatism in a preauthorization trial."* (p1920).

H. NIHR case study- 'The UK as a clinical trials destination: Delivering ground-breaking 'real world' research', 20 May 2019. https://www.nihr.ac.uk/documents/case-study-delivering-real-world-research-the-salford-lung-study/11555

I. National Academies of Sciences, Engineering and Medicine 2019. 'Examining the impact of real-world evidence on medical product development: Proceedings of a workshop series'. Washington DC. The National Academies Press- *demonstrating importance of SLS trial to GSK and that they have taken these methods into other new trials in different medical areas*.

J. European Medicines Agency. EMA Regulatory Science to 2025 Strategic Reflection. Published 2020- *demonstrating increasing emphasis placed on real world evidence by European regulatory body*.