Institution: The University of Manchester

Unit of Assessment: 1 (Clinical Medicine)

Title of case study: Cough monitoring system facilitates clinical trials and enables development of treatments for patients with refractory chronic cough

Period when the underpinning research was undertaken: November 2004 – December 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:
Jaclyn Smith	Clinical Chair in Respiratory Medicine Clinical Academic Consultant	2005 – present 2004 – 2005
Kevin McGuinness	Honorary Research Associate	2008 – present
Ashley Woodcock	Professor of Respiratory Medicine	2004 – present

Period when the claimed impact occurred: 1 August 2013 – 31 December 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

The University of Manchester (UoM), in collaboration with Manchester University NHS Foundation Trust (MFT) and industrial partner Vitalograph, have developed the first accurate system to quantify coughing. The VitaloJAK, built with UoM's algorithm technology has been used in 36 clinical trials to date, increasing the number of studies evaluating cough treatments. It is the only cough monitor approved for use in regulatory clinical trials in Europe and the US and has facilitated the development of the first potential treatment for refractory chronic cough (Gefapixant). Vitalograph's CEO reports revenue of over GBP40,000,000 due to cough monitor adoption which also helped the company create 50 new jobs within UK and Ireland. In addition, it has brought over [text removed for publication] revenue into MFT from royalties, to March 2020.

2. Underpinning research

Context

There is a lack of effective cough therapies, and yet cough is a significant social and physical burden for patients with asthma, chronic obstructive pulmonary disease, pulmonary fibrosis and refractory chronic cough. Failure to develop any novel therapeutics for 50 years is in large part due to the lack of a reproducible, objective test system for coughing. Currently reliance is placed on patient scoring systems/questionnaires. As many cough treatments act on the central nervous system, trial outcomes are influenced by changed cough perception, rather than a real effect on coughing. Cough frequency data is highly repeatable over time and thus a much more powerful endpoint for detecting treatment effects in clinical trials. Therefore, a system to accurately measure cough frequency would improve the ability to study cough mechanisms and facilitate testing of novel therapies for patients.

Cough monitor development

From 2004, a collaboration between UoM, MFT and Vitalograph Ltd led to building, patenting, testing and CE marking (ensuring that the product met EU safety, health and environmental protection requirements), a custom-made digital recording device allowing 24 hour sound recordings. To be of clinical value, signal processing algorithms are essential to

detect and quantify coughing. Smith developed the key algorithm that facilitates counting of coughs by removing non-cough sounds and silence. This and successive improved algorithms have been patented (MFT 2005) and licensed to Vitalograph (current agreement 2017) who market this novel cough monitor as VitaloJAK, supported by underpinning algorithms accessed through the Vitalograph web portal. The details of the algorithms are not published to protect the intellectual property; however data on the methods to quantify coughing and relationships between cough counts and patient reported outcomes were published [1,2].

Application of cough monitor in drug development

UoM collaborated with pharmaceutical companies (including GlaxoSmithKine (GSK), Ariopharma and Afferent Inc) and MFT in applying the cough monitoring system in evaluating novel cough therapies. Early studies established optimal trial design and the statistical power of studies utilising cough monitoring to test therapies. As a consequence of trials using VitaloJAK, mechanisms previously thought to mediate chronic coughing have been discounted; for example, patients with chronic cough characteristically have heightened cough responses to inhaled capsaicin, mediated by the transient receptor vanilloid-1 (TRPV-1) ion channel. However, in a randomised controlled trial, TRPV1 antagonism failed to reduce cough frequency measured with the VitaloJAK [3]. Therapeutic trials (UoM researcher Smith, Chief Investigator) using VitaloJAK cough monitoring, identified a first-in-class P2X3 antagonist (Gefapixant, Afferent Pharmaceuticals Inc.) It is the first highly effective cough therapy in patients with refractory chronic cough [4], reducing cough frequency by 75% over placebo. The cough monitor was instrumental in determining the relationships between drug dose, efficacy and side effects [5], dictating the doses tested in a subsequently positive phase IIb study [6] showing 50 mg twice daily significantly reduced cough frequency (11.3 coughs per hour compared with 18.2 with placebo, a 37% reduction). Phase 3 clinical trials led by Smith are also using the cough monitor as the primary endpoint and recently reported positive findings, indicating this drug has all the attributes to become the first licensed therapy for refractory chronic cough.

3. References to the research

1. Decalmer SC, Webster D, Kelsall AA, **McGuinness K**, **Woodcock A, Smith JA**. Chronic cough: how do cough reflex sensitivity and subjective assessments correlate with objective cough counts during ambulatory monitoring? *Thorax*. 2007 Apr;62(4):329-34. DOI: 10.1136/thx.2006.067413
2. Kelsall A, Decalmer S, Webster D, Brown N, **McGuinness K, Woodcock A, Smith JA**. How to quantify coughing: correlations with quality of life in chronic cough. *European Respiratory Journal*. 2008 Jul;32(1):175-9. DOI:10.1183/09031936.00101307
3. Khalid S, Murdoch R, Newlands A, Smart K, Kelsall A, Holt K, Dockry R, **Woodcock A, Smith JA**. Transient receptor potential vanilloid 1 (TRPV1) antagonism in patients with refractory chronic cough: a double-blind randomized controlled trial. *Journal of Allergy and Clinical Immunology.* 2014 Jul;134(1):56-62. DOI:10.1016/j.jaci.2014.01.038
4. Abdulqawi R, Dockry R, Holt K, Layton G, McCarthy BG, Ford AP, **Smith JA**. P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study. *Lancet*. 2015 Mar 28;385(9974):1198-205. DOI: 10.1016/S0140-6736(14)61255-1
5. **Smith JA**, Kitt MM, Butera P, Smith SA, Li Y, Xu ZJ, Holt K, Sen S, Sher MR, Ford AP. Gefapixant in two randomised dose-escalation studies in chronic cough. *European Respiratory Journal*. 2020 Mar 20;55(3):1901615. DOI:10.1183/13993003.01615-2019
6. **Smith JA**, Kitt MM, Morice AH, Birring SS, McGarvey LP, Sher MR, Li YP, Wu WC, Xu ZJ, Muccino DR, Ford AP; Protocol 012 Investigators. Gefapixant, a P2X3

receptor antagonist, for the treatment of refractory or unexplained chronic cough: a randomised, double-blind, controlled, parallel-group, phase IIb trial. *Lancet Respiratory Medicine*. 2020 Aug;8(8):775-785. DOI:10.1016/S2213-2600(19)30471-0

Prizes and awards

- 2008 North West NHS Innovation Award: Medical Device Category (**McGuinness K, Smith JA, and Woodcock A)**.
- 2010 Distinguished Achievement Award: Researcher of the Year, University of Manchester (**Smith JA)**.
- 2015 NIHR Clinical Research Network, Leading Commercial Principal Investigators Award (**Smith JA**).
- 2019 NIHR Senior Investigator Award (**Smith, JA**).

4. Details of the impact

Context

Chronic coughing is a significant medical problem affecting approximately 12% of the general population, significantly impacting quality of life, with physical, social and psychological burdens, yet currently there are no licensed therapies available. Cough monitoring permits phase 2a studies with just 20-30 patients, allowing proof of concept to be established rapidly and at reduced costs.

Reach and significance of the impact

Adoption in clinical trials and a catalyst for new clinical trials

The VitaloJAK device developed from UoM research is the only cough monitor approved for use in regulatory clinical trials in Europe and US. Without it, many new trials could not have taken place.

Since commercialisation in 2015, the VitaloJAK has been used as a clinical endpoint in 36 clinical trials, recruiting 6,047 patients and analysing 32,569 cough recordings, evidencing how it has catalysed new clinical trials [A].

The EU Clinical Trials registry lists 10 commercial interventional clinical trials in chronic cough in the 10 years prior to its introduction and 19 new trials since the cough monitor's launch in 2015, an increase of 90% [B]. Similarly, the US Clinical Trials registry lists 14 commercial interventional trials from 2005 to 2014, whilst 26 are listed from 2015 onwards, over 85% increase; 16 used the cough monitor and also involved UK sites [C], demonstrating the impacts on trial activity. Merck Research Laboratories' Clinical Research VP explained, "*Cough monitoring provides both drug developers and regulatory bodies with objective evidence that new therapies reduce the amount of coughing experienced by patients, and has changed the standards by which cough therapies are being evaluated*" [D].

Examples of clinical trials seeking new chronic cough treatments and utilising the cough monitor include: NCT02993822 (sponsor Nerre Therapeutics, completed June 2019), conducted at 42 study sites across US/UK, including Manchester; NCT03310645 phase I/IIa trial (sponsor Bayer, completed June 2019) at 7 UK sites, including Manchester; NCT04110054 (sponsor Shionogi Inc, completed December 2020) phase IIb trial completed across 95 sites in US, Europe and Japan [E].

In 2018, Attenua Inc. funded a phase 2a trial NCT03622216 (completed May 2019) evaluating Bradanicline as a cough treatment, employing the VitaloJAK as the primary endpoint. Attenua's CEO said, "*Professor Smith's original and innovative method has given this industry a validated tool that allows us, for the first time, to be able to confidently study new pharmaceutical agents with the potential to treat patients who have no other alternatives to treat their cough.*" [F].

Manchester clinical trials activity has also increased because of the cough monitor availability and expertise in UoM/MFT. In the last 5 years, Smith has recruited 153 patients to 15 clinical studies of potential new therapies, bringing access to new therapies for patients attending the clinical cough service at MFT [G].

Stage III clinical trials to develop a new cough therapy

The largest trials to date are two phase 3 regulatory trials of Gefapixant (Merck). VP, Clinical Research, Merck Research Laboratories stated "*The use of the VitaloJAK cough monitoring system…and Professor Smith's expertise were integral to the phase 2 work performed by Afferent Pharmaceuticals on gefapixant. Since then, Merck has worked with Professor Smith and Vitalograph to use the VitaloJAK system as the primary endpoint in two companion phase 3 trials"* [D]. These studies measured cough frequency in 2,044 participants recruited globally from 171 sites, including 18 sites in the UK (NCT03449134 (completed August 20 /NCT03449147 completed Oct 20). Statistically significant reductions in 24-hour cough frequency for Gefapixant have recently been reported from these trials [H].

Commercial and Economic Impacts

The intellectual property associated with the cough detection algorithm was patented by MFT 'A method for generating output data.' Inventors: Smith, McGuinness, Woodcock. UK Patent Application No. 0511307.1.2015 and licensed to Vitalograph Ltd.

Vitalograph's Chief Executive Officer said "*To date, the VitaloJAK is being used in 36 clinical trials… These studies have ranged from small scale proof of concept studies (n~20-30) to global phase 3 trials (n~1500), working with both small biotechs and large pharmaceutical companies. This work has resulted in over £40 million* [GBP40,000,000] *of revenue for Vitalograph to date… Customers include Merck, Pfizer, GSK, Astra Zeneca, Bayer, Boehringer Ingelheim, Shionogi…. We have also captured 100% of available trials to date"* [A]. Expansion of Vitalograph's clinical trials work, due to the cough monitor, has created new jobs in UK and Ireland. Vitalograph CEO stated, "*In 2017, we invested 12M Euros* (EUR12,000,000) *and created 50 new jobs at our Ennis and Buckingham facilities (data analysts, software designers and engineers) which was in part a result of the collaboration with the University of Manchester in respect of the VitaloJAK, allowing expansion of our clinical trials work, particularly in the treatment of cough"* [A].
MFT receives royalties via the licence agreement from the clinical trials work undertaken using the VitaloJAK cough monitor (income [text removed for publication] to end March 2020) [I].

5. Sources to corroborate the impact

A. Testimonial from Chief Executive Officer, Vitalograph Ltd, 9 October 2020 - ***confirms number of trials cough monitor used in, revenue for Vitalograph and jobs created***

B. Details of commercial interventional clinical trials for chronic cough (not bronchiectasis/COPD) manually selected from EU Clinical trials registry. 01.01.2005 to 31.12.2014 (10 years prior to availability of cough monitor) and 01.01.15 to 30.10.20 – ***demonstrates increased number of commercial interventional EU trials following launch of cough monitor***

C. Details of commercial interventional clinical trials for chronic cough (adult) manually selected from US National Library of Medicine ClinicalTrials.Gov. Chronic Cough related trials 01.01.2005 to 31.12.2014 (10 years prior to availability of cough monitor) and 01.01.15 to 29.10.20 – ***demonstrates an increased number of commercial interventional trials activity following the launch of the cough monitor***

D. Testimonial from VP Clinical Research, Therapeutic Area Head, Respiratory & Immunology, Merck Research Laboratories, 20 October 2020 - ***confirms use of VitaloJAK by Merck and the importance of cough monitoring***

E. Examples of trials which have used the cough monitor – ***cough monitor used by sites in Europe, US and Japan***

F. Testimonial from Chief Executive Officer, Attenua Inc, received 26 October 2020 – ***confirms importance to industry of cough monitor as clinical endpoint and a change to the way therapies are evaluated it has engendered***

G. Details of clinical trials of new potential cough therapies which have taken place in Manchester using VitaloJAK (as at 3 November 2020)- ***allowing Manchester patients access to new potential treatments***

H. Press release from Merck 8 September 2020 https://bit.ly/2JIXSxh ***trials led by Smith using cough monitor show significant decreased cough frequency***

I. Details of royalties received by MFT in respect of VitaloJAK up to March 2020 – ***cough monitor is generating revenue into NHS***