Institution: Queen's University Belfast

Unit of Assessment: 1

Title of case study: Improving outcomes for people with cystic fibrosis through evidence based clinical trials

1. Summary of the impact

New therapies supported by clear evidence from clinical trials have resulted in outstanding improvements in survival and quality of life for people living with cystic fibrosis (CF). Elborn's clinical trials group has delivered a programme of crucial clinical trials which has impacted on clinical practice in CF. From 2009-2012 Elborn co-led a pivotal multicentre trial using Ivacaftor (Kalydeco ™), a transformative new drug which represents a paradigm shift as the first approved therapy that corrects the basic defect in CF. This therapy is an exemplar of personalised medicine and is prescribed for patients with the specific gene mutation in which this drug works.

2. Underpinning research

CF is the most common life limiting autosomal recessive disorder in Caucasian populations. There are over 80,000 people worldwide with the condition, with 10,000 in the UK. Researchers at Queen's University Belfast, led by Elborn, have made major contributions to the understanding of lung disease in cystic fibrosis. This enabled the development of key outcome measures (lung function, exacerbations and nutritional measures) to be used in clinical trials to test new therapies. The group in Queen's, with others, demonstrated in the 2000's that measurements of lung function (FEV1), reductions in pulmonary exacerbations and Quality of Life (QoL) are key outcome measures in clinical trials in order to demonstrate the effectiveness or otherwise of treatments for people with CF[1,2,3]. The validation of these endpoints by the group at Queen's has been crucial to the subsequent and future success of clinical trials in CF. In order for clinical trials to be successfully carried out, the outcome measures have to be clear and be able to be applied correctly and consistently in the participating centres. Research undertaken from 1995 at Queen's validated the importance of measurement of lung function and pulmonary exacerbations as key endpoints in clinical trials in CF and found that these could be applied consistently. These are widely used in clinical trials and are now regulatory endpoints for proof of efficacy in CF trials both used by the European Medicines Agency (EMA) and the US Federal Drugs Agency (FDA).

Elborn's research has made him a world leader in this aspect of CF research. This has been recognised nationally by selection into the **NIHR Respiratory Translational Research Partnership**. The Queen's group is a founder member of this important UK initiative to improve the delivery of early phase clinical trials in lung diseases associated with inflammation and infection. The group is also a founder member of the **European Cystic Fibrosis Society Clinical Trials Network**. This network was initiated and developed by Elborn in his role as President of the European Cystic Fibrosis Society. Both of the above are competitive programmes and success in selection is a mark of excellence and leadership in the area of clinical trials.

The Belfast Centre has participated in 14 international clinical trials undertaken in the past five years in cystic fibrosis and Elborn is international chief investigator on three CF clinical trials currently in progress. Further recognition of his leadership in this field has involved senior authorship of two pivotal consensus statements which have set the agenda for the design and conduct of cystic fibrosis clinical trials in Europe[4,5,6]. Elborn also led a key initiative in European Medicines Agency to provide new guidance for the pharmaceutical industry to develop new

therapies in this condition. This has a major emphasis on acceptable and meaningful outcome measures necessary for regulatory approval and application in the clinic[7].
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/12/WC500136159.pdf

3. References to the research

1. **Elborn JS**, Prescott RJ, Stack BH, Goodchild MC, Bates J, Pantin C, Ali N, Shale DJ, Crane M. Elective versus symptomatic antibiotic treatment in cystic fibrosis patients with chronic Pseudomonas infection of the lungs. Thorax 2000 May; 55(5): 355-8. PubMed PMID: 10770814; PubMed Central PMCID: PMC1745744.
*This investigator led study demonstrated that a widely applied practice of giving intravenous antibiotics was not better than treating when symptoms indicated. Exacerbation rate was used as the primary outcome**.** Funding: British Thoracic Society, £250,000*

2. Balfour-Lynn IM, Lees B, Hall P, Phillips G, Khan M, Flather M, **Elborn JS**; CF WISE (Withdrawal of Inhaled Steroids Evaluation) Investigators. Multicenter randomized controlled trial of withdrawal of inhaled corticosteroids in cystic fibrosis. Am J Respir Crit Care Med. 2006 Jun 15; 173(12): 1356-62. Epub 2006 Mar 23. PubMed PMID: 16556691.
This study demonstrated that inhaled corticosteroids were ineffective in CF. Exacerbations and lung function were validated as key endpoints. Funding: CF trust, £300,000

3. Martin SL., Downey D., Bilton D., Keogan MT., Edgar J., Elborn JS., Recombinant AAT CF study team. Safety and Efficacy of recombinant alpha(1)-antitrypsin therapy in cystic fibrosis. Pediatr. Pulmonol. 2006 41(2): 177-183. PubMed PMID: 16372352
Pivotal clinical trial for transgenic alpha-1 antitrypsin in CF using novel biomarker and clinical outcome measures.

4. Downey DG, Brockbank S, Martin SL, Ennis M**, Elborn JS**. The effect of treatment of cystic fibrosis pulmonary exacerbations on airways and systemic inflammation. Pediatr Pulmonol. 2007 Aug; 42(8): 729-35. PubMed PMID: 17588254.
Paper validating the responsiveness of lung function measurements and limitations of inflammatory biomarkers. Funding PPL Therapeutics £250,000.

5. Döring G, **Elborn JS**, Johannesson M, de Jonge H, Griese M, Smyth A, Heijerman H; Consensus Study Group. Clinical trials in cystic fibrosis. J Cyst Fibros. 2007 Apr;6(2): 85-99. Review. PubMed PMID: 17350898.
Key consensus statement from European CF Society on endpoints in clinical trials.

6. De Boeck K, Bulteel V, Tiddens H, Qagner T, Fajac I, Conway S, Dufour F, Smuth AR, Lee T, Sermet I, Kassai B, **Elborn JS**; ECFS-CTN network partners. Guideline on the design and conduct of cystic fibrosis clinical trials: the European Cystic Fibrosis Society-Clinical Trials Network (ECFS-CTN). J Cyst Fibros. 2011 Jun;10 Suppl 2:S67-74. Doi: 10. 1016/S1569-1993(11)60010-6. PubMed PMID: 21658
Development of 2007 consensus based on a Framework 6 Cost Action, Eurocare CF (€1m). Main output from clinical trials work package.

7. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, Griese M, McKone EF, Wainwright CE, Konstan MW, Moss R, Ratjen F, Sermet-Gaudelus I, Rowe SM, Dong Q, Rodriguez S, Yen K, Ordoñez C, **Elborn JS**. VX08-770-102 Study Group. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med. 2011 Nov 3;365(18):1663-72. Doi: 10.1056/NEJMoa1105185 PubMed PMID: 22047557; PubMed Central PMCID: PMC3230303.

Ground breaking pivotal clinical trial demonstrating the effectiveness of Kalydeco.The primary endpoint was lung function and exacerbations a key secondary endpoint. This agent has now been used to treat 2000 CF patients to date, worldwide.

4. Details of the impact

The research led by Elborn which validated CF trial outcome measures, has had very significant impact on the management of people with CF because the early studies from his group made multicentre trials more reliable, effective and efficient. The validation of clinical trial outcome measures has resulted in evidenced based new treatments for people with CF. In 2007 the Queen's University Belfast and the Belfast Health and Social Care Trust set up the infrastructure to deliver CF trials. This initiative supported the development of an NHS R&D (equivalent in remit to the National Institute of Health Research in England) clinical trials network (CTN) in Respiratory Health in Northern Ireland. This CTN has now successfully completed 26 phase II/III investigator-led and pharmaceutical industry supported clinical trials and has become a major hub for delivery and leadership in clinical trials in cystic fibrosis worldwide. The Centre has now led and contributed to 25 clinical trials in people with CF[1] and is the leading centre in the UK for clinical trials in CF[2].

These trials have allowed optimisation of current anti-inflammatory and anti-infective treatments and have been a contributor to innovative transformative treatments for the underlying basic defect[2, 3] The extensive experience with clinical trials and the CTN infrastructure set up by Queen's and the Belfast Trust resulted in Elborn's group being selected by a number of commercial organisations such as Boehringer, Vertex, Novartis, and Pulmatrix to be the international leads for Phase II and Phase III clinical trials and other interventions in CF. For example, Elborn was the co-Chief Investigator for a ground breaking and landmark study using the first corrective therapy for the underlying defect in patients with CF[4]. Ivacaftor corrects the function of a particular mutation in CF designated as G551D. This mutation in the CF gene affects 5% of people with CF worldwide but 10% of people in Ireland. The drug activates the mutated protein and restores significant function of the defective channel which causes CF in these patients. This Phase III study demonstrated a transformative impact on patients with very significant increases in lung function and quality of life with a concomitant reduction in pulmonary exacerbation[6]. Ivacaftor represents a paradigm shift since for the first time not just the symptoms of CF are treated in the patients but treatment is aimed directly at the cause of the disease. It has now been approved by FDA[5] and EMA[6] and is licensed and funded in USA, UK, Ireland, France and Germany[7]. The outstanding results from Kalydeco led Forbes to select this drug as the most important drug licensed in 2012[9] as it reached sales of $113 million in the first 9 months of the year. This is primarily because Ivacaftor represents a completely new approach to treating people with CF by correcting the basic defect. The very rapid development of this treatment into a prescribed therapy available in the clinic is a consequence of the rapid and efficient execution of the pivotal clinical trial with the appropriate endpoints. Ivacaftor has transformed the quality of life of people with cystic fibrosis who carry the G551D mutation by improving their lung function and nutritional state and reducing the number of exacerbations caused by infection and mucous impaction in the lungs.[10] These are all strong surrogates for survival and it is likely that this therapy will also improve length of life. For those patients who have the G551D mutation this is a transformative therapy. This programme is an exemplar of personalised medicine[5]. The FDA describes the impact of Ivacaftor on people with CF and the exemplar nature of this in the field of personalised medicine as follows: "Kalydeco represents an excellent example of the future of personalised medicine…..it is part of a revolution in how we will treat patients in the future". This pivotal trial with Ivacaftor has also for the first time demonstrated that the CFTR protein is a drugable target and correction of function results in transformative clinical benefit. This has very significant societal impact for

people with cystic fibrosis demonstrating real future hope that a wide range of mutations may indeed be treatable. This is evidenced by a range of major pharmaceutical companies developing potentiator and corrector programmes as this target is now attractive (Novartis, Pfizer, Bayer). Elborn is an advisor of study designs of the programmes with Novartis and Bayer and a CI on the Novartis and Bayer programmes.

5. Sources to corroborate the impact

1. List of Queen's clinical trials and link to clinical trials databases. http://clinicaltrials.gov/
2. Letter from Cystic Fibrosis Trust
3. Letter from European Clinical Trials Network (www.ecfs.eu/ctn)
4. Letter from European Cystic Fibrosis Society
5. Letter from Vertex
6. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002494/WC500127780.pdf
7. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm289633.htm
8. http://previous.cftrust.org.uk/pressoffice/pressofficepo/kalydeco_updates/kalydeco_eng_win
9. http://www.bbc.co.uk/news/uk-northern-ireland-21760928
10. http://www.forbes.com/sites/matthewherper/2012/12/27/the-most-important-new-drug-of-2012/
11. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/12/WC500136159.pdf