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Use of a Rare Disease Patient Registry in the conduct of Long-term Post-Authorisation Drug Studies.

A Model for Collaboration with Industry

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Traditional development of novel therapeutics assesses product risks and benefits in Phase III trials. When questions remain, licensing may be deferred whilst clarification is sought. To help deliver new medicines to patients sooner, Post Authorisation Safety Studies (PASS) and Post Authorisation Efficacy Studies (PAES) have been introduced by medicines regulators. Regulators recognise the efficiencies of registries to deliver these studies and the use of established patient registries is encouraged by the European Medicines Agency (EMA)(1).

Patient or disease registries are typically developed by the clinical community. Whilst not usually designed for post authorisation safety/effectiveness evaluation, they may be adapted for this purpose and have the benefit of providing longer term understanding of a specific disease (2). Treatment registries developed by pharmaceutical companies usually provide specific post authorisation data limited to the timeframe of the request.

Cystic Fibrosis is found in 1 in 2200 people in the UK with 90% now detected by newborn screening enabling detailed monitoring from birth. Median life expectancy is currently 47 years of age. The UK Cystic Fibrosis Registry (UKCFR) , with records of over 10000 patients, is sponsored by the UK Cystic Fibrosis Trust. With appropriate authorisations and consent, data representing 99% of the UK CF population are entered by care teams in all UK CF Centres. (5) Data is collected from multiple disease domains (demographics, diagnosis, complications, mortality, laboratory data, nutrition, pulmonary function, respiratory microbiology, physiotherapy) with a summary reported annually (6).In 2015 the UKCFR passed an audit against Good Pharmacoepidemiology Practice standards.

We report a model for successful partnership with industry in the conduct of post authorisation studies, utilising a rare disease patient registry. Our five year experience demonstrates the potential for improving the quality of pharmacovigilance by utilising the unique strength of a registry study - the ability to compare exposed and unexposed patients in cohorts matched for key characteristics. In this paper we examine the key components of the model.

Our pharmacovigilance programme began in 2012 and was initiated by EMA requests to three companies, to develop long term safety studies for cystic fibrosis products. In the same year, the EMA produced guidelines and templates for PASS protocols and final reports (3) and in 2015 for PAES (4). Key opportunities which influenced the decision to support this initiative was the potential for improving the methodology of long term safety studies and for engaging and encouraging industry involvement in cystic fibrosis therapeutics.

The principal components of the CF Trust Pharmacovigilance Model are:

- A UK Lead Investigator, who is an appropriate CF physician, provides independent clinical guidance and Registry expertise to industry partners and the EMA in the development of the study protocol, and contributes to the interim and final reports.
- Senior Statisticians, independent of the marketing authorisation holder (MAH), contribute to the development of the study protocol and statistical analysis plan, conduct analyses and draft reports. EMA designated formats are adopted for reporting of summary anonymised data (7).

- Pharmacovigilance programme support, to construct delivery plans for interim and final reports, and agree timelines, through drafting to final version (approximately 2-3 months). The MAH submits reports to the EMA, sharing feedback with the UKCFR to enable changes to the analysis for subsequent reports.

The Trust has worked with professional NHS R&D and legal advisers to develop a standard Services Agreement between the Trust and the MAH. The main provisions of the Agreement are in Panel 1.

| Panel 1: Study Services Agreement Provisions | |
|---|---|
| Engagement: | Clear exposition of the services to be provided, in accordance with the Study Protocol |
| Study Governance: | Parties comply with all applicable laws, statutes and guidance of EU and UK |
| Confidentiality: | Non-disclosure of personal data and patient-level data in study reports Company and Cystic Fibrosis Trust business confidentiality |
| Intellectual Property: | The Trust grants a licence to the Company for access to anonymised data analysis and resulting reports only |
| Stated Use | Summary data reports to be used only for the agreed and stated purpose of a PASS/PAES |
| Publication: | Provisions to ensure that results of scientific interest are published in the public domain |
| Funding: | The financial agreement between the Trust and the MAH ensures that the company covers all the costs of conducting the study and that none of the work is subsidised by either the Charity or the NHS. Each company pays a set-up fee to cover the costs incurred by the Trust in adding any new variables to the UKCFR, and the preparatory work needed to agree the study protocol and the service agreement. The services funded during the length of the study include a contribution to the costs of data collection within CF Centres, provided in the form of grants from the Trust, and the full costs of project management, analysis and reporting |

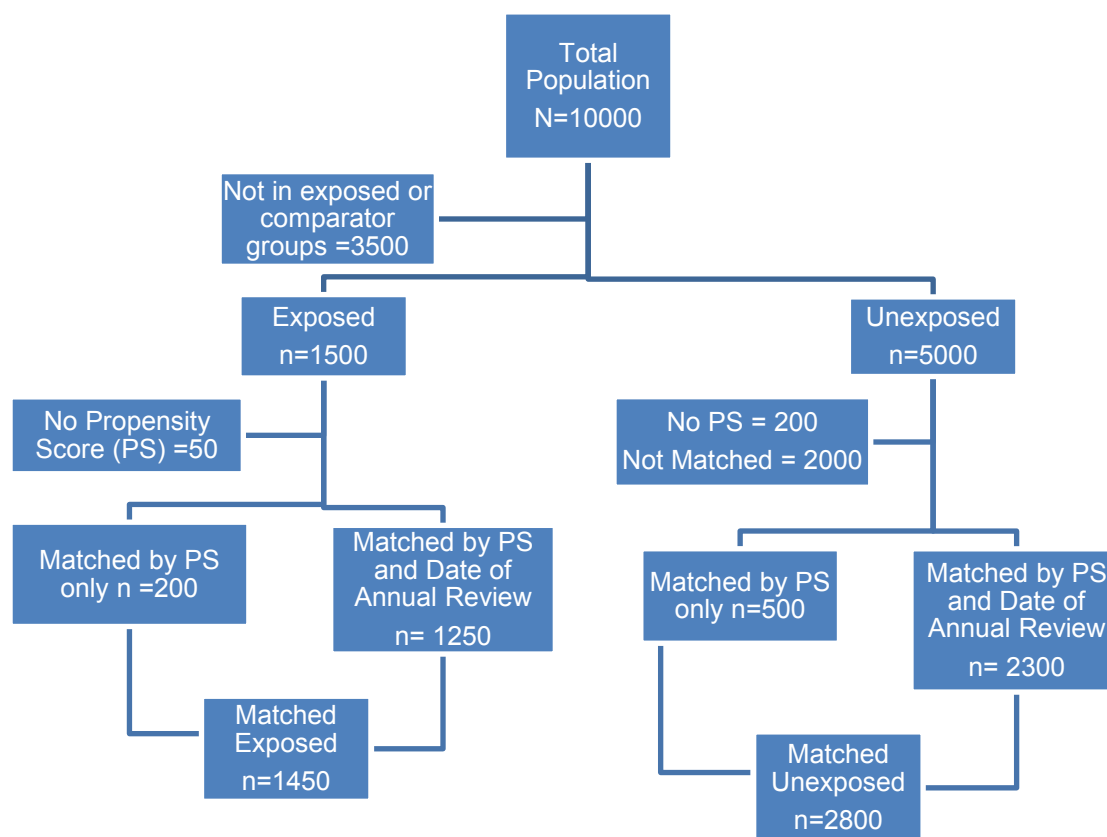
Funding to support the pharmacovigilance programme has driven improvements in the Registry and enabled a financial contribution to be made to UK CF Centres to facilitate data entry. The resulting enhancements to the UKCFR, particularly in medication dates and patient outcomes, have been of benefit to other researchers using the Registry, and to the NHS in monitoring the impact of new drugs.

The most important element in study design is the ability to capture information on all users of the medicine in a real world situation, which can include “off label” use and those patients with mild or severe disease who are often excluded in the randomised control trial (RCT)

setting. Adverse effects of new compounds highlighted in RCTs may readily be targeted for enhanced surveillance but a disease registry provides the ability to capture a broader range of events over several years of exposure. The ability to compare exposed and unexposed patients in cohorts matched for key characteristics is a significant strength of patient registries, and pre-defined comparator groups (usually selected using a propensity scoring system) allow longitudinal tracking of outcomes. Studies should commence at point of medicine authorisation to have optimal opportunity to capture safety/effectiveness in the population.

In Figure 1 is an example of a study flowchart, beginning with the whole UKCFR patient population, through the stages of selection of the study groups and a typical matching process to end up with the final groups for analysis.

Figure 1 Study Cohorts Flowchart



A summary of the current studies in the programme is provided in Table1. The Observational Study to Evaluate the Long-Term Safety of Ivacaftor in Patients with Cystic Fibrosis, commenced in the UK in 2013, has reported interim results (8).

Table 1

| MAH | Pharmaxis Ltd | Vertex Pharmaceuticals (UK) Limited | Forest/Teva | Vertex Pharmaceuticals (Europe) Limited | Chiesi Pharmaceuticals |
|-------------------|--|---|---|--|---|
| Medicinal Product | Bronchitol™ | Kalydeco® | Colobreathe® | Kalydeco® | Quinsair® 240 mg nebuliser solution |
| Timeline | 2012-2017 | 2013-2017 | 2014-2019 | 2016-2022 | 2017-2021 |
| Study | PASS | PASS | PASS | PAES | PASS |
| EU PAS Reg. No. | 20668 | 4270 | 16395 | | 20990 |
| Design | Observational comparative cohort study | Observational comparative cohort study | Observational comparative cohort study | Observational comparative cohort study | Observational comparative cohort study |
| Exposed Group | Adult (≥ 18yrs) Bronchitol treated patients | Ivacaftor treated patients (≥ 6 yrs) | Colobreathe treated patients | Kalydeco treated patients aged 2-5 yrs at therapy initiation | Quinsair treated patients |
| Comparison Groups | a) Matched Non-Bronchitol treated patients b) Full unexposed population | Patients with no evidence of Ivacaftor exposure | Patients treated with other inhaled anti-pseudomonal antibiotics. | Patients with no evidence of Ivacaftor exposure | Patients treated with other inhaled approved antibiotic therapies |
| Matching | Propensity score and date of annual review | CFTR genotype class, age and gender | Propensity score and date of annual review | CFTR genotype class, nutritional status, age and gender | |

In the development of registry- based post authorisation studies, MAHs have channelled communications between registry holders and regulators. However the EMA is now recommending that they liaise more directly with disease registry holders at an early stage in the development of study protocols. This is intended to improve clarity on what information is needed and what is available. The UKCFR endorses early engagement to avoid unrealistic expectations and to facilitate early implementation for any additional registry data fields that may be required. Improved communication should significantly shorten the current 12-18 months timeline for agreeing study protocols, speeding up study completion and reporting.

The recent Life Sciences Industrial Strategy (9) urges the development of more national patient registries, particularly in rare or orphan diseases, actively supported by patient charities. The UK government has agreed to the implementation of the UK Strategy for Rare Disease (10) which calls for better use of rare disease registries in research and development. The UKCFR has developed a successful model for partnership with industry to conduct long term safety and efficacy studies, aimed at improving the safety of medicines and the quality of pharmacovigilance. It is hoped that this ground-breaking experience will prove of value to organisations holding registries or developing new ones in response to these strategies, and will be of interest to pharmaceutical companies and trade associations, in advancing the quality of real world studies, to the benefit of patients.

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