OpenApp Registry

The Evolution of a Patient Registry

> The European Commission services fully agree with patients' organisations and healthcare professionals that disease registries are "an indispensable infrastructure tool for translating basic and clinical research into improved care and therapeutic solutions".
>
> Dominique Ristori Director-General Joint Research Centre European Commission

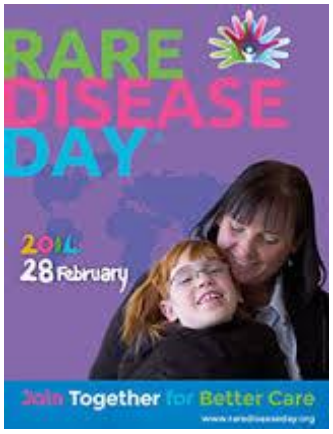
Introduction

Patient registries constitute key instruments for the development of clinical research and the improvement of patient care and healthcare planning as well as quality of life outcomes; "If it can be measured it can be managed".

Patient registries store highly personal and sensitive information. The confidentiality of the information must be guaranteed. Allowing access to patient registries data without breaching confidentiality requires thought and planning.

OpenApp's vision

Most modern hospitals are moving from paper based systems to computerised systems. These EHR (Electronic Health Record) systems are designed to integrate all the disparate functions of a hospital into one unified paperless system. Vendors such as McKesson, Cerner and Epic charge tens of millions of Euros per hospital. However most of these hospital systems end up as independent information silos where critical information on rare diseases cannot be shared between hospitals.



A disease is officially considered rare when it affects fewer than 5 in 10,000 citizens. Between 6,000 and 7,000 different rare diseases have been identified to date; affecting more than 60 million people in Europe and the US alone. Rare diseases tend to be ignored by traditional health care systems but when rare disease providers and patients are interconnected in the online world a very strong value added community can emerge. Registries at the centre of this community can be really powerful because they help consultants and specialists by giving them access to real time norms.

Registries are optimised for one disease and are not limited by geographical area. Using OpenApp Registry™ , registries can integrate with multiple hospital based labs and radiography departments. Doctor's notes, multi disciplinary team reviews and automated assessment triggers can be integrated into the registry giving a longitudinal view of each patient's disease history along with real time comparisons to health factor norms. With

OpenApp Registry , a registry can become a virtual Electronic Health Record (EHR) system highly optimised around the target disease and not limited by a hospital's geographical reach.

The evolution of a patient registry

Most patient registries start life as a simple spreadsheet. Over a period of time features are added to meet user demands. This evolves into a tangle of interrelated spreadsheets commonly referred to as "spreadsheet hell".

OpenApp have years of experience in patient registries and health care data reporting and can help clients take their registry through this evolution process.

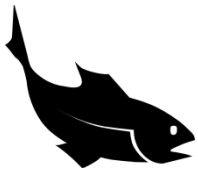
Stage 1 the single cell organism (the spreadsheet registry)

- Patient demographic and disease dataset set up as columns in a spreadsheet.
- Single user standalone system.
- Forms are very primitive.
- Reporting is manual and challenging.
- Data quality is very hard to manage
- "Spreadsheet Hell"

Stage 2 Multi cell organism (multi user access)

- Comprehensive form designer supporting multiple assessment forms at point of contact e.g. Children and Adult
- Intuitive user interface requiring minimal training for non technical clinicians
- Data entry validated at the time of input
- Context sensitive help
- Look up fields/ drop down boxes with system administrator configurable valid icd-10, drug treatments and disease classification entries
- Support for migrating historical data
- Support for attaching letters, including scanned documents, to a patient record
- Identify and flag records with missing critical fields
- Duplication detection and data record merging. Automated merging based on user definable rules. Unmerge/rollback in the event of an erroneous merge
- Comprehensive record searching and querying options
- Pre defined automated reports graphs and export data files (.xls) for users with preapproved access.

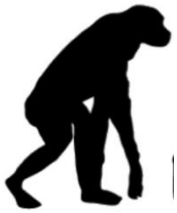
Stage 3 Backboned animals (adding structure)



- Secured confidential access to patient's record. The registry guarantees the protection of confidential data whilst maximising the reuse of data by all stakeholders.
- Role based access control
- Sys admin can set up time based access for locum staff and real time remote log off for terminated staff
- Data Protection approved methodologies to ensure identification of the patient at point of contact but de-identification (Anonymisation) of data for all aggregation and sharing purposes

- Compliance with Freedom of Information requests and Health Record Retention standards
- Support multiple electronic and manual patient consent models
- Comprehensive audit trails with user date, time stamping of all updates, queries and deletions along with a general user activity log
- National and cross border data protection legal compliance
- Registry oversight: Governance and custodian definitions
- Automated backup, business continuity and disaster recovery systems

Stage 4 Benefits of the Group (communication)



- Support international nomenclature standards ICD-10, SNOMED CT and Orpha codes for rare disease classification to allow pooling of harmonised data.
- Cloud or on premise hosting;
- secure web or tablet access
- Integration with labs, radiology, pharmacy through HL7 web services
- Hospital EHR integration. Integration with episode of care transactions
- Bulk update and review of records from hospital systems.
- European data integration following different data protection standards allowing comparison of quality of care across vastly different health systems

Stage 5 Intelligence (the registry evolves into a decision support system)

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- Quality Assurance against European, national and local norms.
- Multidisciplinary team reviews
- Support cohort studies
- Increased standards of care by automating assessment triggers and integrating alert manager. This allows manual and automated alerts to schedule follow up treatments. The system provides for date/time stamped acknowledgement of alerts.
- Automated drug interaction notification
- Comparative medical observations. The clinical provider gets immediate feedback on observations and measurements – previous value, min/max value etc.
- The registry models the natural history of the disease and becomes a computerised clinical decision support system optimising the patient care.
- The registry becomes a virtual Electronic Health Record (EHR) system highly optimised around the target disease and not limited by a hospital's geographical reach.

Planning a patient registry

What are you trying to accomplish?

The answer to this question is key to the definition of the data dictionary and all of the elements to be collected, the extent of quality control required, and the analytic skills necessary to make valid scientific use of the data

> Where well-implemented registries and active patient organizations exist, the likelihood for developing a treatment for the disease in question is increased.
> *Orphanet. Report on Rare Disease Research, Its Determinants in Europe and the Way Forward, May 2011*

Data Set definition

BNDMR The French rare disease program has made significant investment in rare disease research. They have published a very effective minimum data set for rate disease registries which OpenApp follow. It is divided into

1) Personal information
2) Consent,
3) Family relationships
4) Vital stats
5) Care pathway
6) Care activities
7) Disease history
8) Diagnosis
9) Diagnosis confirmation
10) Treatment
11) ANTE and neonatal
12) Research

This minimum data set should be expanded to include extra fields to track the disorders history and other life style factors.

Making data reusable and interoperable

The creation of an in-house dictionary of ICD-10, SNOMED-CT and Orpha codes will allow every aspect of care to be captured as coded data rather than free text. This can include for example past and present diagnoses, histories, examinations, microbiology, genetics, physiology, interventions, medications, allergies and pathology. These codes can be hidden behind templates, allowing live data to be captured in a standard form for all users.

Encouraging data collection

One ongoing problem with registries is encouraging doctors to contribute. In hospitals this is easy because they normally batch update their records monthly. Registries requiring regular updates by GPs a large number of data collection points e.g. Asthma are challenging. The best type of data is collectable in a short time, binary (male or female, alive or dead), quantitative with high precision (genetic type, height weight, etc.) and predictive of outcome. Desired variables should be ranked in order of importance, ease of collection and meaningful analysis based on unambiguous definitions.

To encourage participation the output from the registry should be of assistance to personnel charged with providing the data. OpenApp Registry includes real time graphical reporting which give the clinical an immediate return on investment. A general principal should be that clinicians cannot get access to the data if they will not contribute to maintaining its accuracy.

Data Entry

Tablets and browsers allow encounter based data entry from multiple remote sources. This not only saves enormous time and money over paper based forms, but provides immediate feedback to the clinician and patient in the event that data entered is abnormal. This abnormality can be flagged as an error or a warning requiring immediate intervention.

US research overview

The Office of Rare Disease Research is a division of the US National Institute of Health . They have defined the common data elements (CDE) for rare diseases which acts as the minimum data set for a rare disease registry. The CDE definition encourages data collection using standard nomenclature such as:

- **SNOMED CT** provide clinical descriptions for diseases, clinical findings, and procedures.
- **LOINC** is the standard for transmitting laboratory and clinical observations in HL7 messages.
- **PROMIS**; Patient-Reported Outcomes Measurement Information System (PROMIS). These questionnaires help standardise the measurement of a patients state of wellbeing or suffering as well as their ability or lack of ability to function.

By defining data elements and standardising health care nomenclature, the NIH has released a global rare disease data repository (GRDR) where anonymised (de-identified) patient data can be aggregated in a standardised manner.

Patient health information is protected by HIPAA in the US. This comprehensive Act of 1996 makes all parties involved in storing and processing patient information liable for ensuring strict level of security.

The US FDA (Food and Drug Administration) has also specified how electronic health care records need to be protected and how electronic signatures can be used to replace hard copy signatures (referred to as 21 CFR Part 11).

EU research overview

The Council of the European Union has recommended that each member country:

1) prepare a rare disease national action plan
2) establish national centers of expertise to concentrate support in the field of rare diseases.

Many patient organisations receive registry funding from these government organization, through for example Horizon2020 grants.

Regulations concerning registries are in early stages in most European countries. No guidelines are available yet on best practices for exchanging and sharing data.

The European Commission Joint Research Centre JRC is actively developing a European platform for Rare Disease Registration. This EU standard will be defined by the European Committee of Experts on Rare Diseases (EUCERD). This will probably use disease naming conventions specified by Orphanet and adopt a data set such as the French National Minimum Data Set for Rare Diseases v1-08.

European data protection regulations are generally more onerous that North American. Countries like German and Switzerland even have controls over personal data being transferred across internal states/cantons. However there is currently no restriction on sharing data that has been properly anonymised (de-identified). Designing a registry that is compatible with US and EU regulations,

classification and data protection standards remains a challenge.

Because data protection standards are highly developed and different in the US and Europe we would recommend setting up at least two registers one in Europe and one in the US. Data can be anonymised for sharing between registries.

Anonymisation code of practice

Personal data elements such as name, address, date of birth etc are easy to remove when anonymising and not likely to be required for research or studies. However certain personal fields are clearly important for research but can aid the re-identification process: Age, country, clinician and hospital information, ethnic background. It is our general recommendation that if any query produces a dataset of five or less records then further anonymisation should be performed. For example replace age (e.g. 54) with aggregated age group (50-59). OpenApp follow the anonymisation code of practice as published by the UK Information Commissioner in 2012.

Pharma Interest

Pharma companies have little interest under normal market conditions in developing and marketing drugs intended for only a small number of patients suffering from very rare conditions. However they will often get a conditional market authorisation for orphan drugs which obliges them to establish a clinical trial stage IV post marketing follow-up. This is traditionally through using their own drug registry software.

A preferable solution is to use an established patient registry provided it has the flexibility to add extra data elements required for the trials and secure that data on behalf of the Pharma company. OpenApp Registry has a flexible data structure and security model that fully supports this as well as the ability to import data (XML, CSV) from other registries. This removed the need for duplicated data entries and cuts down on training and consolidation costs.

Sources of funding

In many cases it takes years to realise the full benefits of a patient registry as it develops to include many new EHR features and models the disease history. Most registry owners have a limited budget for their register. Because OpenApp Registry is an open source system, OpenApp can normally deliver a basic registry system to match the available budget and to allow registry owners to demonstrate a working valuable system to their funders.

Registry documentation, training and feedback

Adequate documentation is essential for ensuring the quality and efficient operation of the registry. A non technical guide to the registry should be available for patients. Regular user training should be budgeted for. System evaluation through questionnaires will help calculate cost savings and understand system deficiencies.

Industry Best Practices

EURORDIS European Rare Disease Organization

NORD National Organization for Rare Disorders

CORD The Canadian Organization for Rare Disorders

EURORDIS-NORD-CORD Joint Declaration

The 10 Key Principles for Rare Disease Patient Registries

1. Patient Registries should be recognised as a global priority in the field of Rare Diseases.

2. Rare Disease Patient Registries should encompass the widest geographic scope possible.

3. Rare Disease Patient Registries should be centred on a disease or group of diseases rather than a therapeutic intervention.

4. Interoperability and harmonization between Rare Disease Patient Registries should be consistently pursued.

5. A minimum set of Common Data Elements should be consistently used in all Rare Disease Patient Registries.

6. Rare Disease Patient Registries data should be linked with corresponding biobank data.

7. Rare Disease Patient Registries should include data directly reported by patients along with data reported by healthcare professionals

8. Public-Private Partnerships should be encouraged to ensure sustainability of Rare Disease Patient Registries.

9. Patients should be equally involved with other stakeholders in the governance of Rare Disease Patient Registries.

10. Rare Disease Patient Registries should serve as key instruments for building and empowering patient communities

European Committee of Experts on Rare Diseases (EUCERD)

Core Recommendations on Rare Disease (RD) Patient Registration

1. RD patient registries and data collections need to be internationally interoperable as much as possible and the procedures to collect data elements need to be harmonised and consistent, to allow pooling of data when it is necessary to reach sufficient statistically significant numbers for clinical research and public health purposes.

2. All sources of data should be considered as sources of information for RD registries and data collections, to speed up the acquisition of knowledge and the development of clinical research.

3. Collected data should be utilised for public health and research purposes.

4. Patient registries and data collections should adhere to good practice guidelines in the field.

5. Existing and future patient registries and data collections should be adapted to serve regulatory purposes, where required.

6. Patient registries and data collections should be sustainable for the foreseeable time span of the registries' utility.

The European Commission has long proposed in its Communication "Rare Diseases: Europe's Challenges" that Member States gather national data on rare diseases and pool it together with European counterparts

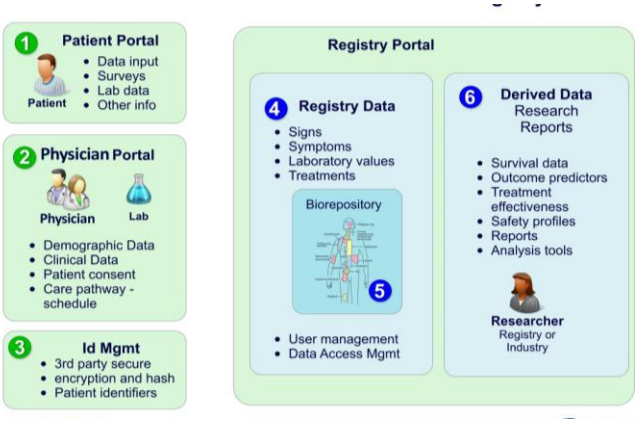
mHealth Data Integration

In a consumer-driven patient-centered healthcare model, patients will play a greater role in tracking their health through mobile health apps that monitor vital information such as medication adherence, blood pressure, and glucose readings.

In the era of smart mobile phones and mHealth apps and devices patients want to actively manage their own disorders.

Separate Patient and Clinician registries

OpenApp's approach is to separate the patient owned data elements from the clinician owned data elements. The patient controls what data is shared with the clinician and the clinician controls the date shared with the patient. Thus the clinician is not responsible for the content or accuracy of patient controlled data. More importantly the clinician / physician is not responsible for monitoring data entered through the patient portal minimizing the potential of litigation. The patient portal is based on the open source PCHR system developed by Boston Children's Hospital – Indivo.



Interoperability

in other words sharing data across borders. Because the disease population in each country is low this is critical.

PARENT cross-border PAtient REgistries iNiTiative.

OpenApp supports PARENT the cross-border PAtient REgistries iNiTiative. The aim of this project is to rationalise and harmonise the development and governance of patient registries, thus enabling cross border comparisons of vital registry data. It will:

- Provide European wide health indicators for rare diseases.
- Enable a reduction of inequalities between member states in treatment of patients with rare diseases.

Proactive Care Management

Patients want to integrate alert messages and manage follow up appointments. They want the registry to become a much more proactive health management tool recording and managing quality of life issues for patients.

Patient Vs. Drug Registry

The UK based European Medicines Agency (EMA) www.ema.europa.eu, generally expects Pharma companies to set up a **drug registry** for Phase IV clinical trials. This is also know as post-marketing surveillance for orphan medicinal products.

These are designed to measure real world safety and effectiveness of the drugs They know the drug can work and want the registry to prove that they really do work in practice.

> Registries should be organised around population health needs rather than around a therapeutic intervention.
>
> *EUCERD Recommendations*

> The European Commission services fully agree with patients' organisations and healthcare professionals that disease registries are "an indispensable infrastructure tool for translating basic and clinical research into improved care and therapeutic solutions".
>
> Dominique Ristori Director-General Joint Research Centre European Commission

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

A drug registry, or product registry, has a clear purpose and a clear lifespan (typically very short). The data collected can be regarded by Pharma companies as proprietary and not shared with clinicians in general.

A patient registry has a longer time frame and broader goals. Many Patient Registries have existed for 20 years or more and are ideal for longitudinal or epidemiological studies.

A "**patient care**" registry not only focuses on drug treatment but also optimal quality of life issues for patients with a rare disease / disorder. OpenApp believe that patient care registries that follow guidelines for treatments and model the natural history of the disease / disorder are the best structure for new registries to follow.

A long term Patient Care registry should also allow patients to be able to use registry data to qualify health centers of excellence based on their historic performance. This goal was recently endorsed by the National Institute for Health and Care Excellence (NICE) in the UK.

OpenApp Registry allows a short term drug product registry to be set up as a subset of the main patient care registry. This is achieved by extending the data sets and reports to cater for the clinical trials requirements . It is even possible to define the extent to which the proprietary data collected by the Pharmacy company is anomonised and made available to third parties.

Protection of patient privacy

Patient registries store highly personal and sensitive information. The confidentiality of the information must be guaranteed. Allowing access to patient registries data

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without breaching confidentiality requires thought and planning.

Is the Cloud secure?

In the era of internet everywhere the public in general have embraced using their phone or computer browser to access and manage their highly confidential bank accounts. Records in OpenApp Registry can be set up to have the same level of security as an online bank account.

In reality no system is 100% secure. A "Snowden" type administrator with system level access can always copy patient records whether they are on a database or in the cloud. However through managing role based password access the registry operators can ensure that the security of their cloud based system matches that of a desktop system.

Consent requirement

> Of great importance for patients and families, the consistent longitudinal collection of patient data facilitates the creation of standards of care and dramatically improves patient outcomes and life expectancy even in the absence of new therapies.
>
> *Eurordis.org publications "rare disease patients experience and expectations"*

The ethical principle of respect for persons supports the practice of obtaining individuals' consent to the use of their health information for research purposes. This includes consent to registry creation by the compilation of patient data, consent to the initial research purpose and uses of registry data, and consent to subsequent use of data by the patient registries developer or others, for the same purpose or other research purposes.

Individuals (children and parents included) should be informed about the type of research that might be carried out, the arrangements for access to or sharing of stored information, and the duration of storage. The consent process should also include instructions about the way to withdraw at any time.

It is OpenApp's experience that a properly managed consent process will encourage a very high participation rate (in excess of 95%).

Transparency

Transparency contributes to public and professional confidence in the scientific integrity and validity of registry. Registry owners achieve transparency by making the patient registries objectives, governance, sources of data and of funding, available to anyone. Creating a website describing all these elements is one way to achieve transparency.

Oversight

The patient registry owner can be the sole decision-maker, but usually there is a governing board including all stakeholders: the data providers, the patient organisation(s), the funding agency, the professionals running the patient registries (clinical researchers, statisticians, information technology specialists). It is also desirable to appoint an independent advisory board to provide oversight of registry operations, particularly regarding the scientific independence.

Data Ownership or Custody

The concept of ownership does not fit health information comfortably as it fails to acknowledge individual patient privacy interests in health information. However, the legal concept of custody is useful. Custodians have legal rights and responsibilities, among which is to preserve privacy and dignity of individual patients. Custody is also transferable from one custodian to another, which is particularly relevant for patient registries which are long-term projects. Policies should be based on the following principles:

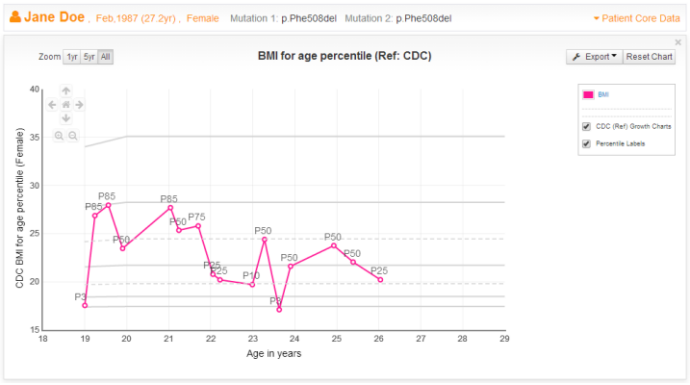
- The subject should always be considered as a primary controller of its data and information directly derived from it. Once the information has been processed, it becomes research data (i.e. data) unless there is agreed private ownership. The processor and/or principle investigator of data should be considered as the guardian of the data. As such, it is up to this person to take all the appropriate steps to protect the data, its storage, use and access. It follows that the researcher holds ultimate intellectual property with due consideration for benefit sharing data.

- Use of collections by third parties should be allowed providing that there is no transfer of ownership and that the use is in agreement with the present guidelines. Patient registries can also receive Copyright protection as they satisfy the statutory definition of a compilation.

Audit Trails

Date and time-stamped audit trails ensure the trustworthiness, integrity and reliability of the records and database. Any change (including deletions) made to a record contains a complete time stamp and includes the user login information. Audit trails are essential in the event of a data breach or a challenge to the data protection procedures of the registry.

Advantages of Open Source



Registry owners have typically used third parties to develop stand alone database applications based on their original spreadsheet models. After a few years these become very difficult and expensive to upgrade.

OpenApp believe that just like medical research innovative software should be shared . Open source is in fact a very good model for Health Care. Open source provides registry owners with three distinct advantages:

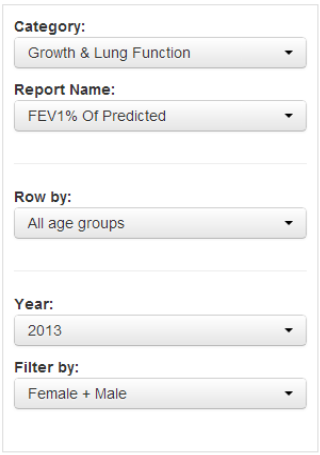
1. Ownership of their system. With full access to the source code they can enhance or upgrade the system as they see fit.
2. An independent market for ongoing maintenance and development. They will not be locked into a proprietary software maintenance contract. If a client is not happy with their maintenance and support, they are free to use a third party.
3. A cost effective development platform with no software licensing costs. Up to 50% of the costs of health care projects can be software licenses. All OpenApp charge for is professional time.

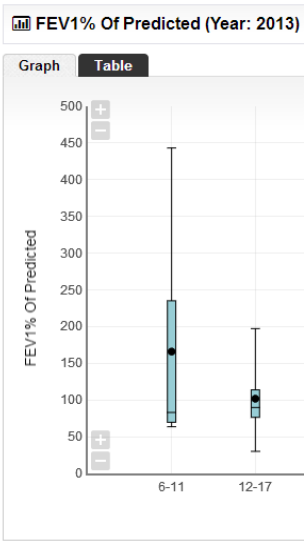
Case Study: European Cystic Fibrosis Society

In March 2013, OpenApp welcomed six members of the European Cystic Fibrosis Patient Registry to sign and commence the development project for their new registry (ECFSTracker based on OpenApp Registry). OpenApp

beat off competition by way of tender and a presentation session with the design of a customised OpenApp eHealth product. ECFSTracker is a customisation of the Boston Children's Hospital PHR project with additional Django features.

ECFSTracker was officially launched at the European Cystic Fibrosis Society's Winter Meeting in Jan 2014.





ECFSTracker collects and reports anonymised patient data across twenty three countries in Europe improving patient monitoring and care. Additionally the platform allows each patients encounter at their CF centre to be monitored and tracked, with helpful patient charts to interact and discuss progress between doctor and patient.

ECFSTracker is a data collection and reporting tool which resolves many of the issues experienced with traditional offerings including ease of access to highly confidential patient records, local customisations of data schema and form layouts along with built in reporting at all levels of data collection The application is developed around a customised version of the Boston Children's Hospital PHR project with further Django additions. It is browser based, and remotely managed reducing reliance on local hospital IT. Is has a simple user interface requiring minimal training.

""OpenApp was selected by an open competition process to be the technology provider for the ECFSR. To date we have been impressed with their professionalism in handling a very complex project which has involved developing and implementing a pan European solution. They embraced the project with enthusiasm and not really seen as a supplier but as part of the team working to develop the best possible solution. I look forward to working with them further in developing additional functionality and modules to the core European solution for our Irish Registry. This technology is state of the art and has great potential in any Registry environment" Godfrey Fletcher Technical Steering Committee; ECSFR..

OpenApp Background

OpenApp is a leader in the deployment of open source software in Health Care Providers and have delivered dozens of applications over the past 12 years.

OpenApp have been selected on the basis of its unique health care expertise as a client of the Health Innovation Hub

Health Innovation Hub

OpenApp specialises in collecting and reporting health care data. This has lead to the development of OpenApp Registry . This product has been designed to provide a platform for disease registries. Years of domain knowledge provide sophisticated real time and statutory

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reporting geared to the requirements of health care clients.

Many health care providers underestimate the importance of patient confidentiality and security when they move to an online solution. OpenApp Registry supports sophisticated multiuser role based security systems with full audit trails and anonymising of demographic data. In addition OpenApp can advise on issues such as patient consent, transparency, oversight governance and data ownership.

OpenApp work with large health datasets on a hospital and national level within the confidentiality and security requirements :

- Family Doctor Prescribing
- Hospital Encounter Activity – diagnosis and procedures – Emergency Department – Laboratory and Imaging - Patient Administration
- Service information – locations, providers, services, capacity
- Population data and deprivation and age weighted cohorts
- NQAIS (National Quality Assurance Intelligence System) projects have similar reporting needs of ICDS and are deployed or under development in Histopathology, Endoscopy, Emergency Medicine, Family Doctor Prescribing, Hospital Mortality and Hospital Elective Surgery.

OpenApp has invested heavily in acquiring health domain knowledge through on all aspects of health service monitoring and management, epidemiology studies in partnership with health academics and Electronic Health Record (in partnership with IBM and DSS Inc in Florida).

OpenApp has developed a number of data analysis and visualisation tools to aid in the dissemination and interpretation of data including interactive charts, pivot tables, maps and symbolisation.

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http://www.eucerd.eu/EUCERD/upload/file/RDTFReportRegistriesJuly2011.pdf

http://www.orpha.net/ The portal for rare diseases and orphan drugs

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