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Registries as a source of Real World Evidence (RWE)

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Dr Stella Blackburn

Disclaimer

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The views expressed should not be taken to represent the views of my former employer: the European Medicines Agency.

- Definition of a registry
- Different types of registries
- What evidence are we trying to generate?
- Use of registries throughout the product life-span
- EMA’s registry initiatives

Registries


BIZARRO.COM
Facebook.com/BizarroComics
Dist. by King Features
It's not listed on their registry, but have you considered a sesame seed toaster?
©DAN PIRARO
3.27.17

Registry

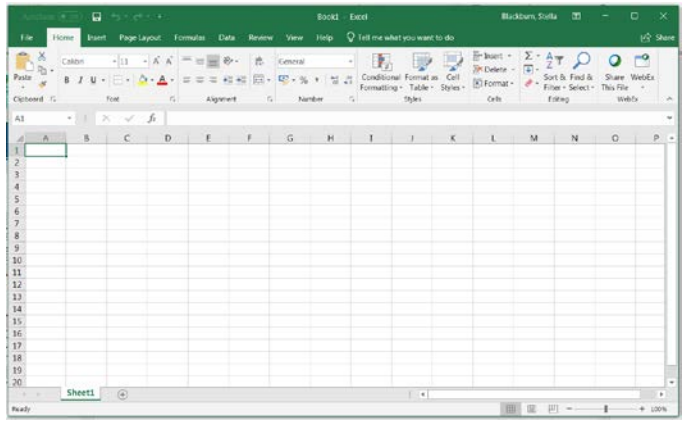
An organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure.

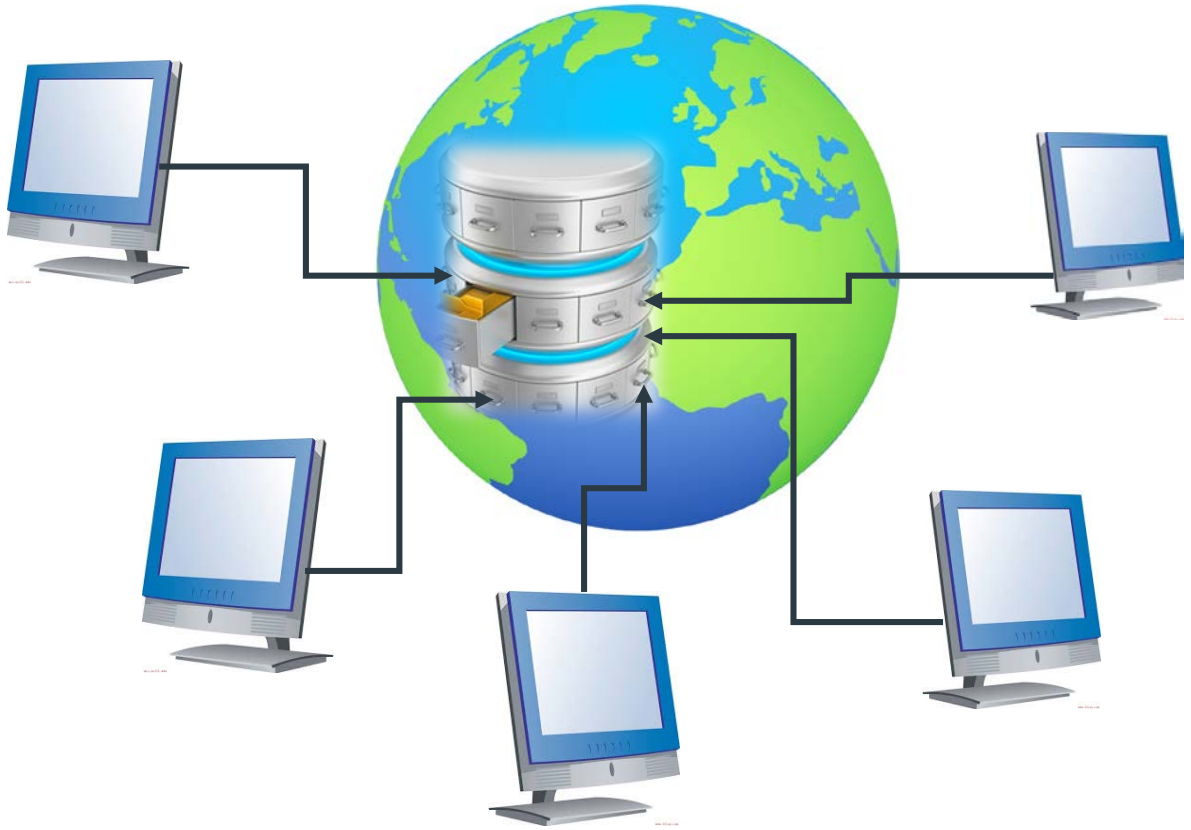
Annex 1 to GVP: Definitions EMA/876333/2011 (rev.4)

A patient registry is an organised system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes.

AHRQ - Registries for evaluating Patient Outcomes: A user's guide

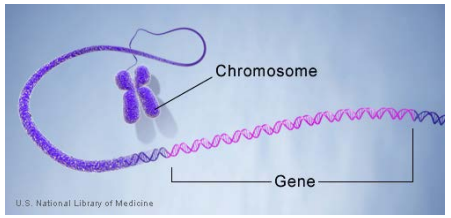
Registries – the big, the small and the ugly



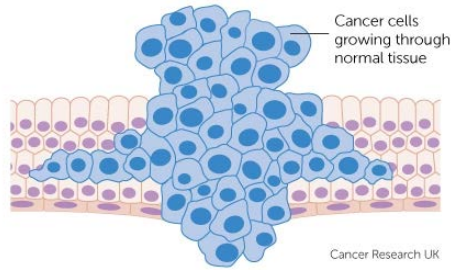


Classification of registries

- Product registries

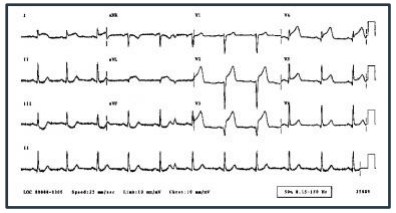


- Disease registries

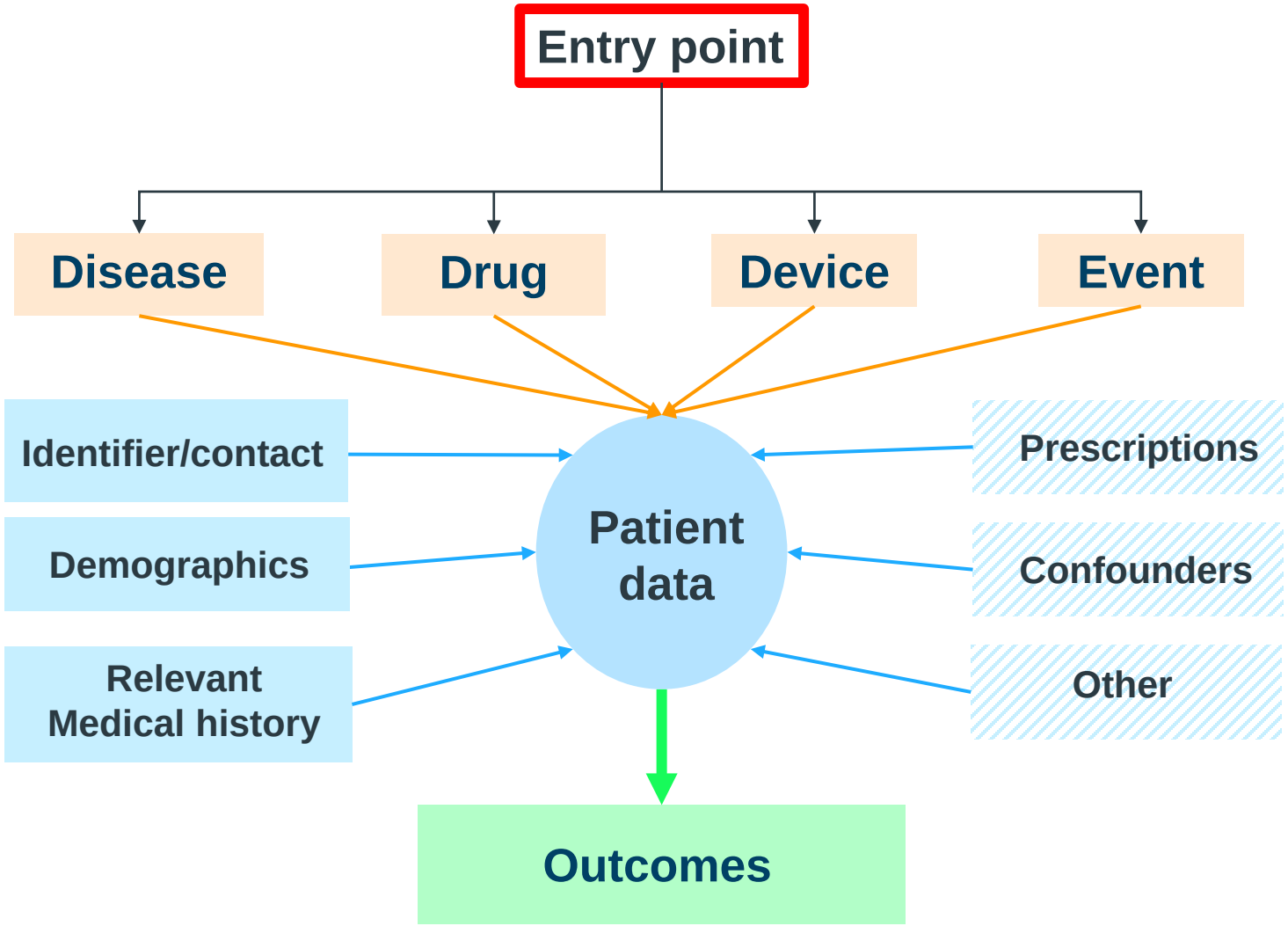


- Procedure or health services registries

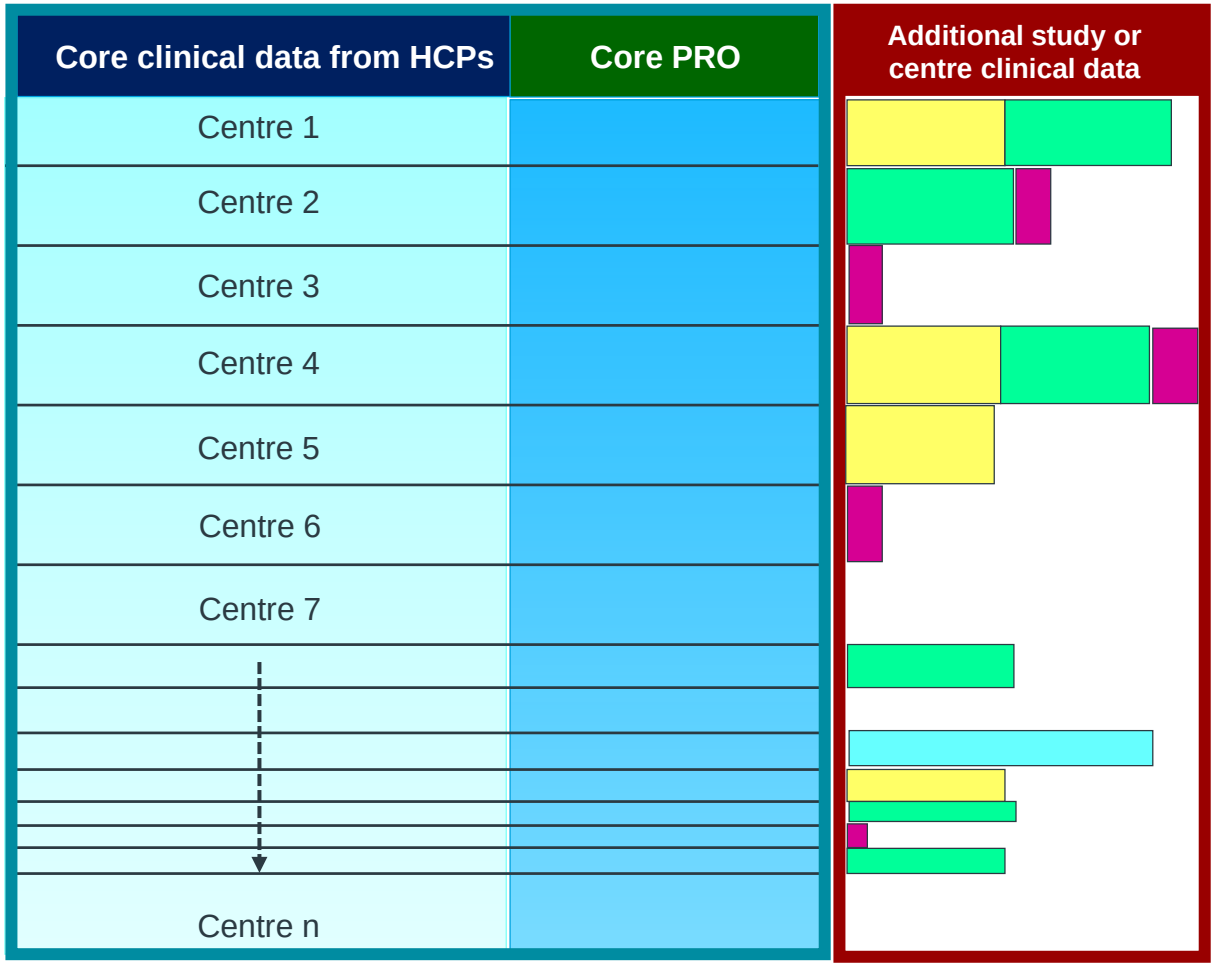
  ≈ Event



Data types in a registry



Registry as a core for scientific research



Extra data collected by centres with patients enrolled in clinical trial 1

Extra data collected by centres with patients enrolled in clinical trial 2

Extra data collected by centres with patients enrolled in PASS

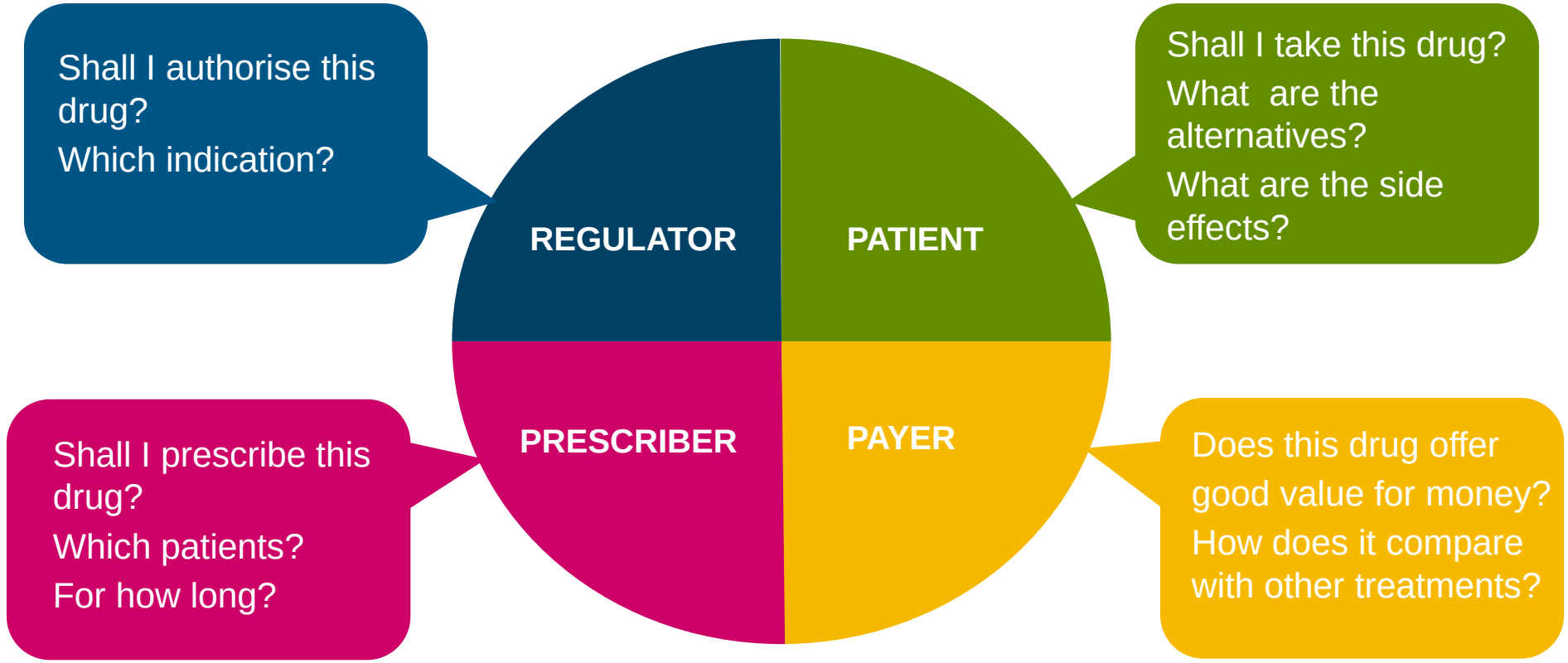
Extra data collected by physician with own research programme

George Orwell
1945

Evidence

Why do we need evidence?

Who makes which decisions?



Different stakeholders need different evidence!

Use of registries

Uses of registries for evidence generation: early

	Regulator	HTA body/ Payer	Provider	Patient	Sponsor
Disease epidemiology	X	X	X	X	X
Patient journey		X	X	X	X
Existing treatments	X	X	X	X	X
Unmet medical need	X	X			X
Identify biomarkers	X	X	X		X
Burden of disease	X	X	X	X	X
Resource use		X	X		X
Co-morbidities	X	X	X		X

Use of registry data to get information on disease epidemiology

- Who gets this disease?
  - Demographics
  - Are there variants of the disease – eg spinal muscular atrophy
- What are the risk factors/causes for this disease?
  - Different genetic mutations,
  - Hypertension, hyperlipidaemia etc for Myocardial Infarction
- What is the natural history of the disease?
  - Relapsing/remitting
  - Progressive
  - Moving between degrees of severity (eg critical limb ischaemia)

Use of registry data as external comparator in initial EU MA

Situation

Metastatic Merkel Cell Carcinoma (MCC)

Procedure

Initial marketing authorisation for avelumab

Issue

RCT not possible

Data

88 patients from a Phase II single arm open label study of avelumab compared with retrospective data from 20 patients in a US Oncology network and 34 patients in a EU MCC Registry undergoing chemotherapy

Results

Overall estimated mean survival for 2nd line avelumab was 12.9 months. Overall median survival was 4.4 months US vs 5.3 months EU for 2nd+ line chemotherapy. BOR for 1st line avelumab was 71.4%. BOR for 1st line chemo was 31.3% US vs 29.4% EU

Outcome

“Taking into account the intrinsic limitation of single arm studies, the rarity of the disease and the challenges to compare the results with data from historical controls and in the literature, the currently available data are deemed to support the efficacy of avelumab in both pre-treated and chemotherapy-naïve patients.”

CHMP Public Assessment Report EMA/496529/2017

Uses of registries for evidence generation: later

	Regulator	HTA body/ Payer	Provider	Patient	Sponsor
Drug utilisation	X	X			X
Long term f/u outcomes	X	X	X	X	X
Overall effectiveness	X	X	X	X	X
Identification of predictors of effectiveness/efficacy	X	X	X	X	X
Identification of adrs	X	X	X	X	X
Identification of risk factors for adrs	X		X		X

Studies required by EMA for gene therapy products

Name Date authorised	Indication	Vector	Studies	Final report date
Glybera 25/10/2012 (expired)	Adult patients with familial LPLD, confirmed by genetic testing, with detectable levels of LPL protein suffering from severe or multiple pancreatitis despite fat restriction	AAV1 + CMV promotor, woodchuck hepatitis post transcriptional regulatory element + AAV2	1. LPLD registry (cat 1) (+ untreated patients) 2. Assessment of immune response at baseline, 6 months and 12 months in a clinical study (cat 3) 3. Clinical study to provide chylomicron metabolism data in 12 new patients and healthy volunteers (cat 3) 4. LTFU of study CT-AMT-011-01	Not stated Dec 2017 Not stated Rolled over into registry at end of trial.
Strimvelis 26/05/2016	Rx of patients with ADA-SCID for whom no suitable HLA-matched stem cell donor is available.	Replication deficient gama-retroviral vector	1. Registry (cat 1) of patients treated with Strimvelis 2. LTFU of patients from study AD115611 (cat 3) (patients also being rolled over into registry) 3. Effectiveness of educational material (cat 3) 4. Methodology to investigate retroviral insertion site analysis (cat 3)	Q4 2037* Q1 2020 Q1 2021 Q4 2024
Luxturna 22/11/2018			1. Non-interventional PASS in disease registry of patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations (cat 1) 2. 15 year follow up of patients in the clinical programme (cat 1)	30 June 2030 31 Dec 2031

LPLD = lipoprotein lipase deficiency; ADA-SCID = adenosine deaminase deficiency severe combined immunodeficiency; LTFU = long term follow-up

European Medicines Agency Registry Initiatives

EMA initiative on patient registries

Launched September 2015

Aim: To provide an adequate source of post-authorisation data for regulatory decision making

- To make better use of existing registries
- Facilitate the establishment of high quality new registries if no suitable existing ones

Actions: Inventory of patient registries

Cross Committee task force

Patient Registries workshop

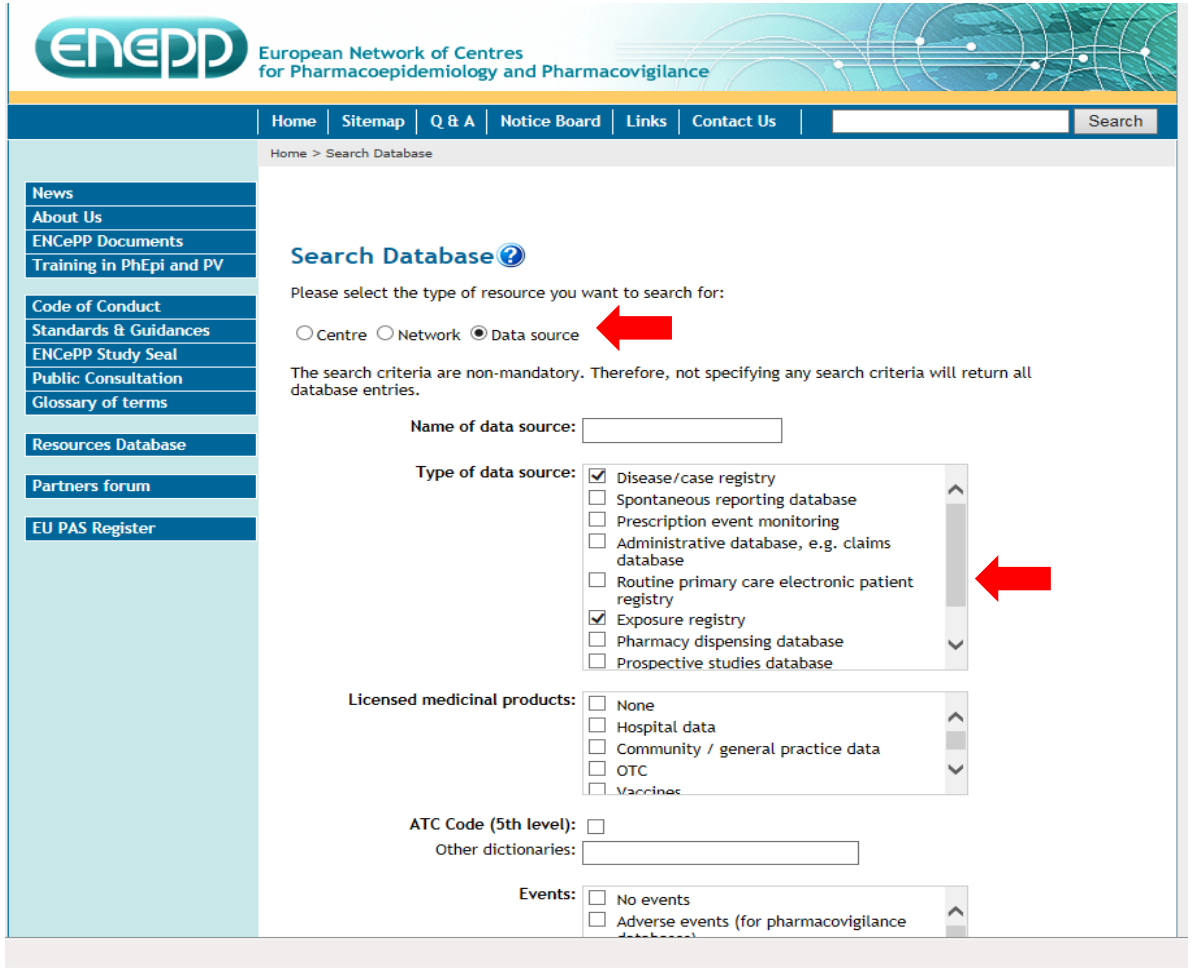
Disease specific workshops

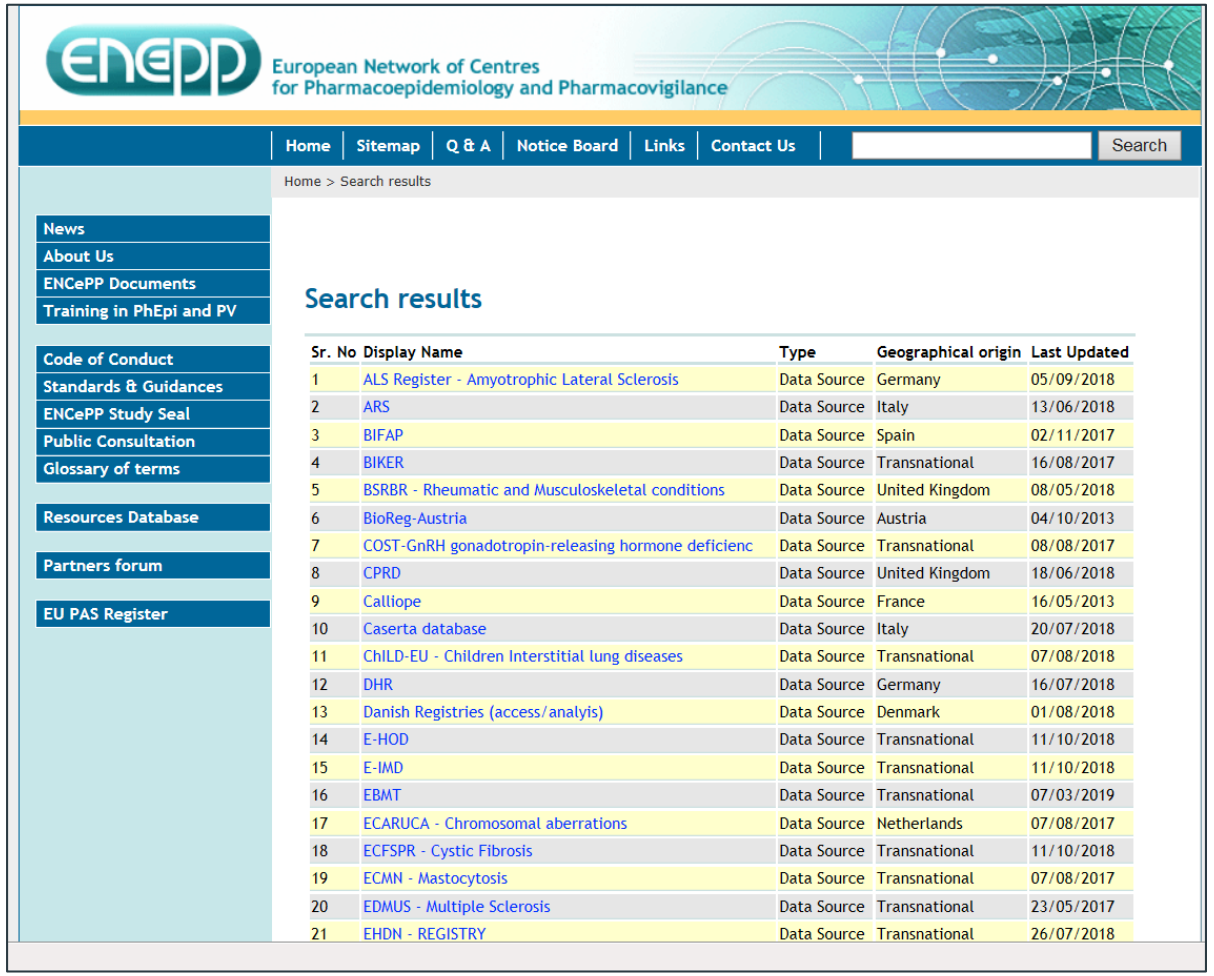
- Haemophilia
- Chimeric antigen receptor (CAR) T-cell therapy
- Multiple sclerosis
- Cystic fibrosis

EMA Inventory of Registries

http://www.encepp.eu/

Finding registries in the ENCePP Resources Database

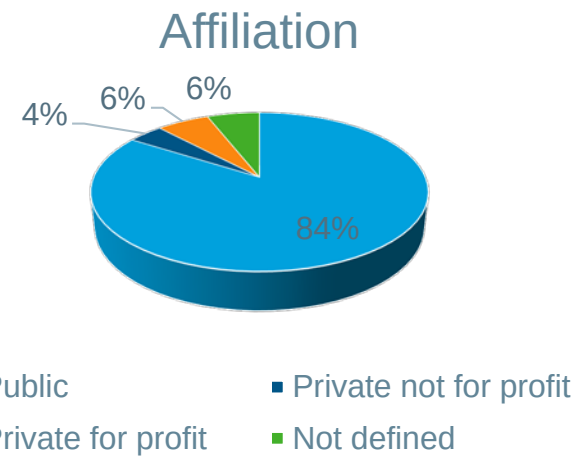




Sr. No	Display Name	Type	Geographical origin	Last Updated
1	ALS Register - Amyotrophic Lateral Sclerosis	Data Source	Germany	05/09/2018
2	ARS	Data Source	Italy	13/06/2018
3	BIFAP	Data Source	Spain	02/11/2017
4	BIKER	Data Source	Transnational	16/08/2017
5	BSRBR - Rheumatic and Musculoskeletal conditions	Data Source	United Kingdom	08/05/2018
6	BioReg-Austria	Data Source	Austria	04/10/2013
7	COST-GnRH gonadotropin-releasing hormone deficienc	Data Source	Transnational	08/08/2017
8	CPRD	Data Source	United Kingdom	18/06/2018
9	Calliope	Data Source	France	16/05/2013
10	Caserta database	Data Source	Italy	20/07/2018
11	ChILD-EU - Children Interstitial lung diseases	Data Source	Transnational	07/08/2018
12	DHR	Data Source	Germany	16/07/2018
13	Danish Registries (access/analyis)	Data Source	Denmark	01/08/2018
14	E-HOD	Data Source	Transnational	11/10/2018
15	E-IMD	Data Source	Transnational	11/10/2018
16	EBMT	Data Source	Transnational	07/03/2019
17	ECARUCA - Chromosomal aberrations	Data Source	Netherlands	07/08/2017
18	ECFSPR - Cystic Fibrosis	Data Source	Transnational	11/10/2018
19	ECMN - Mastocytosis	Data Source	Transnational	07/08/2017
20	EDMUS - Multiple Sclerosis	Data Source	Transnational	23/05/2017
21	EHDN - REGISTRY	Data Source	Transnational	26/07/2018

Orphanet: Rare disease registries in Europe

- 7000+ rare diseases
- 747 rare disease registries in the EU +
- 686 rare diseases included



COUNTRY	REGIONAL	NATIONAL	EUROPEAN	GLOBAL	TOTAL
AT - Austria	3	24	6	3	36
BE - Belgium	2	14	1	2	19
BG - Bulgaria	0	8	0	0	8
CH - Switzerland*	1	12	1	6	20
CY - Cyprus	0	2	0	0	2
CZ - Czech Republic	0	5	0	0	5
DE - Germany	10	88	8	39	145
DK - Denmark	1	5	0	0	6
EE - Estonia	0	2	1	0	3
ES - Spain	11	43	2	1	57
FI - Finland	0	7	0	0	7
FR - France	20	109	16	6	151
GR - Greece	0	3	0	0	3
HR - Croatia	0	2	0	0	2
HU - Hungary	0	5	0	1	6
IE - Ireland	4	12	0	1	17
IL - Israel*	0	2	0	0	2
IS - Iceland*	0	2	0	0	2
IT - Italy	11	54	3	7	75
LT - Lithuania	0	1	0	0	1
LU - Luxembourg	0	1	0	0	1
LV - Latvia	0	1	0	0	1
MK - Republic of Macedonia*	0	1	0	0	1
MT - Malta	0	2	0	0	2
NL - Netherlands	1	14	5	10	30
NO - Norway*	0	4	3	0	7
PL - Poland	3	6	1	0	10
PT - Portugal	5	11	0	0	16
RO - Romania	0	2	0	0	2
RS - Serbia*	0	4	0	0	4
SE - Sweden	0	14	1	3	18
SI - Slovenia	0	2	0	0	2
SK - Slovakia	0	2	0	0	2
TR - Turkey*	0	5	0	0	5
UA - Ukraine*	0	1	0	0	1
UK - United Kingdom	5	48	11	15	79
TOTAL	77	518	59	93	747

https://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf

Conclusions

- Registries are an organised system that use observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure.
- The most common types are disease or product registries
- They can vary in size, complexity and geographical location
- They are designed for a specific research purpose
- To be useful, the data need to be of sufficient quality and to contain the data elements of interest.
- They have multiple uses both pre - and post – authorisation