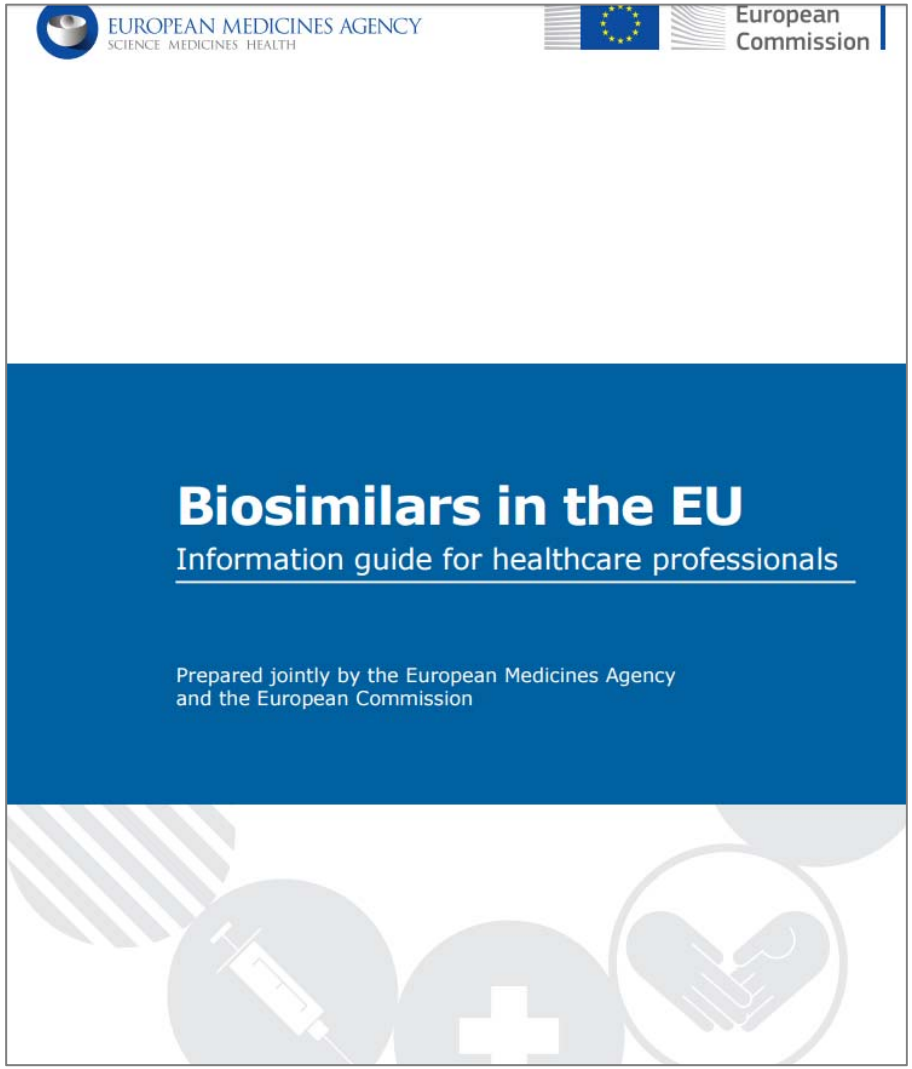
DIEP Lazio
Dipartimento di Epidemiologia
Servizio Sanitario Regionale
Regione Lazio

SISTEMA SANITARIO REGIONALE
ASL ROMA 1

REGIONE LAZIO

Analisi dello switch fra principi attivi all'interno di categorie terapeutiche

Switch: biosimilari



EMA and Member States' responsibilities

When EMA carries out the scientific review of a biosimilar, the evaluations do not include recommendations on whether the biosimilar is interchangeable with the reference medicine, and thus whether the reference medicine can be switched or substituted with the biosimilar.

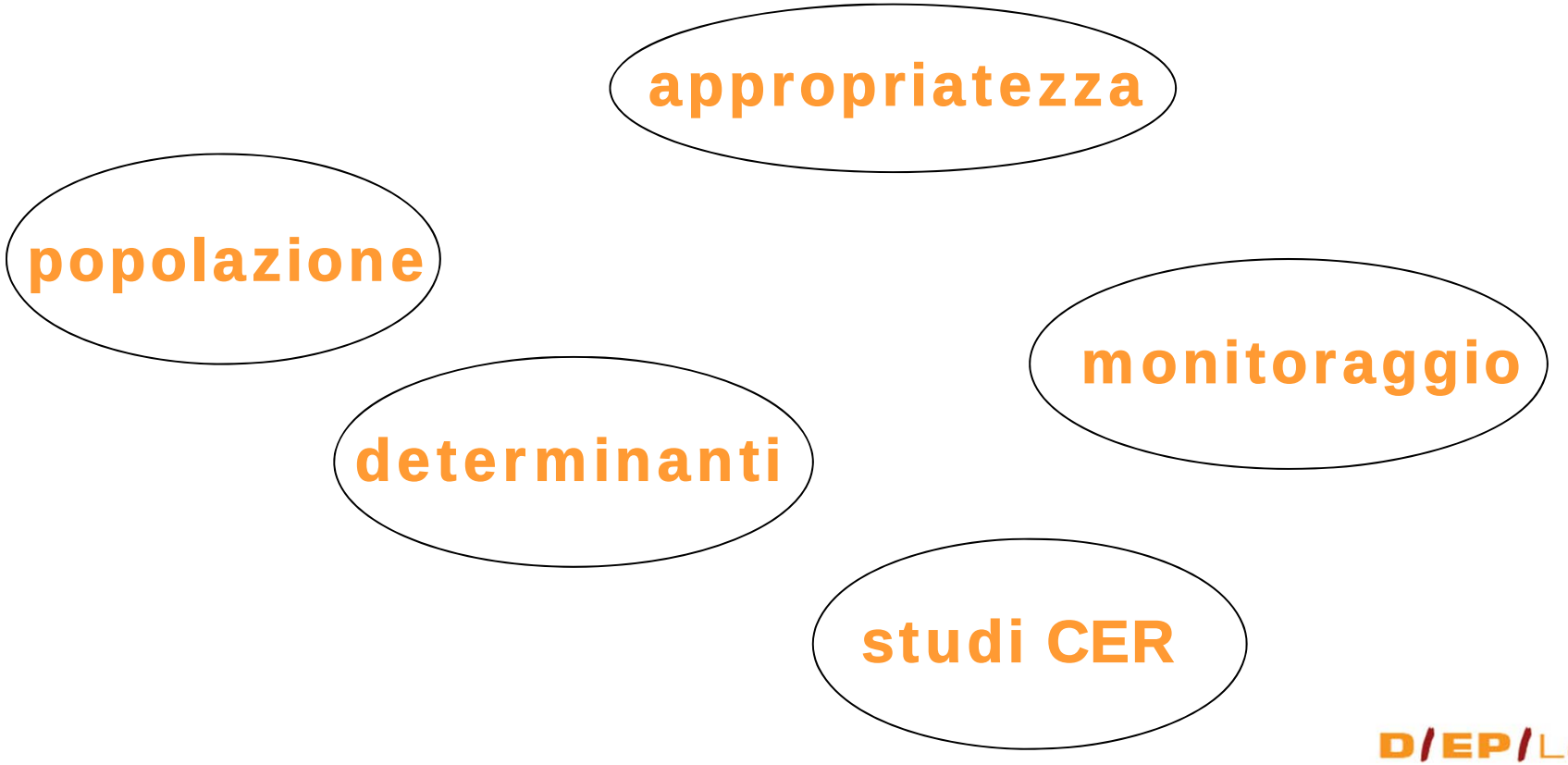
The decision on whether to allow interchangeable use and substitution of the reference biological medicine and the biosimilar is taken at national level. Information on the scientific evaluation performed by EMA's scientific committees is available on EMA's website and could be used to support decisions.

Any decision on switching should involve the prescriber in consultation with the patient, and take into account any policies that the country might have regarding the prescribing and use of biological medicines.

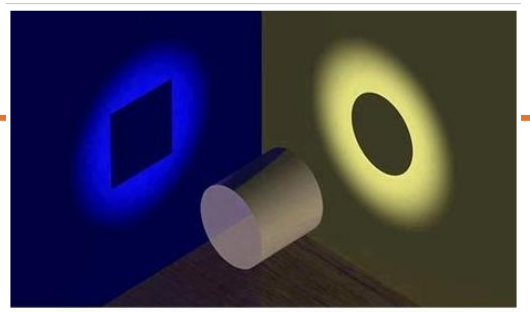
EMA does not regulate **interchangeability, switching and substitution** of a reference medicine by its biosimilar. These fall within the remit of EU Member States.

Switch: non solo biosimilari

Lo switch farmacologico o drug switching è molto diffuso in pratica clinica, soprattutto nel management delle patologie croniche, e si riferisce alla sostituzione di un farmaco con un altro.



Switch: problemi aperti



Quando cambi il modo di osservare le cose, le cose che osservi cambiano.

1. Definizione:
   - switch tra molecole
   - switch tra specialità
   - switch tra dosaggi/modalità di assunzione

2. Problemi di numerosità/complessità/setting

3. Tempo allo switch

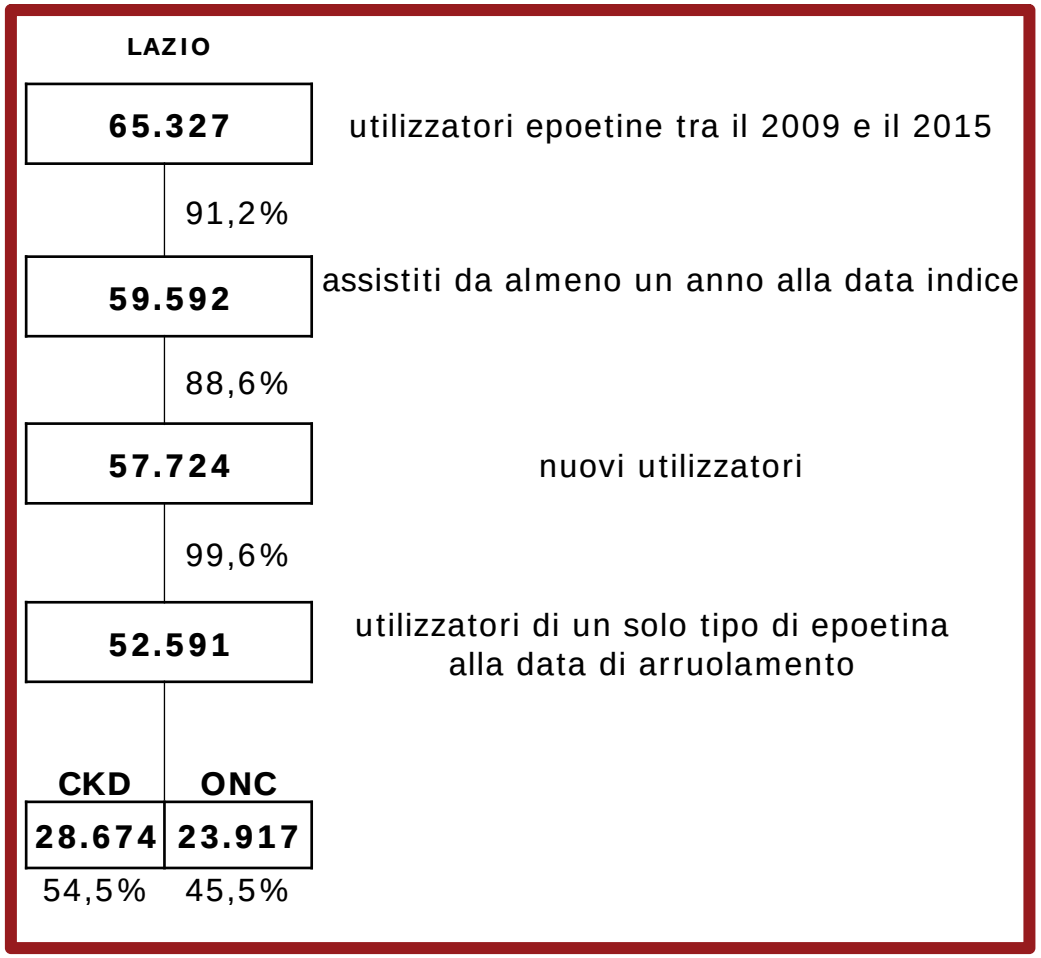
4. Ragioni dello switch

5. Switching back/multiple switching

Switch: esempi

- Switch tra epoetine
- Switch tra immunosoppressori
- Switch tra follitropine

Switch: epoetine



Epo_Alpha: Eprex
Epo_Biosi: Abseamead,Binocrit, Retacrit
Epo_Long: Mircera, Aranesp
Epo_Short: Eporatio, Neorecormon

	CKD		ONC	
	28674		23917	
Epo_Alpha	6662	23%	9371	39%
Epo_Biosi	696	2%	1546	6%
Epo_Long	18139	63%	9969	42%
Epo_Short	3177	11%	3031	13%

Switch: epoetine

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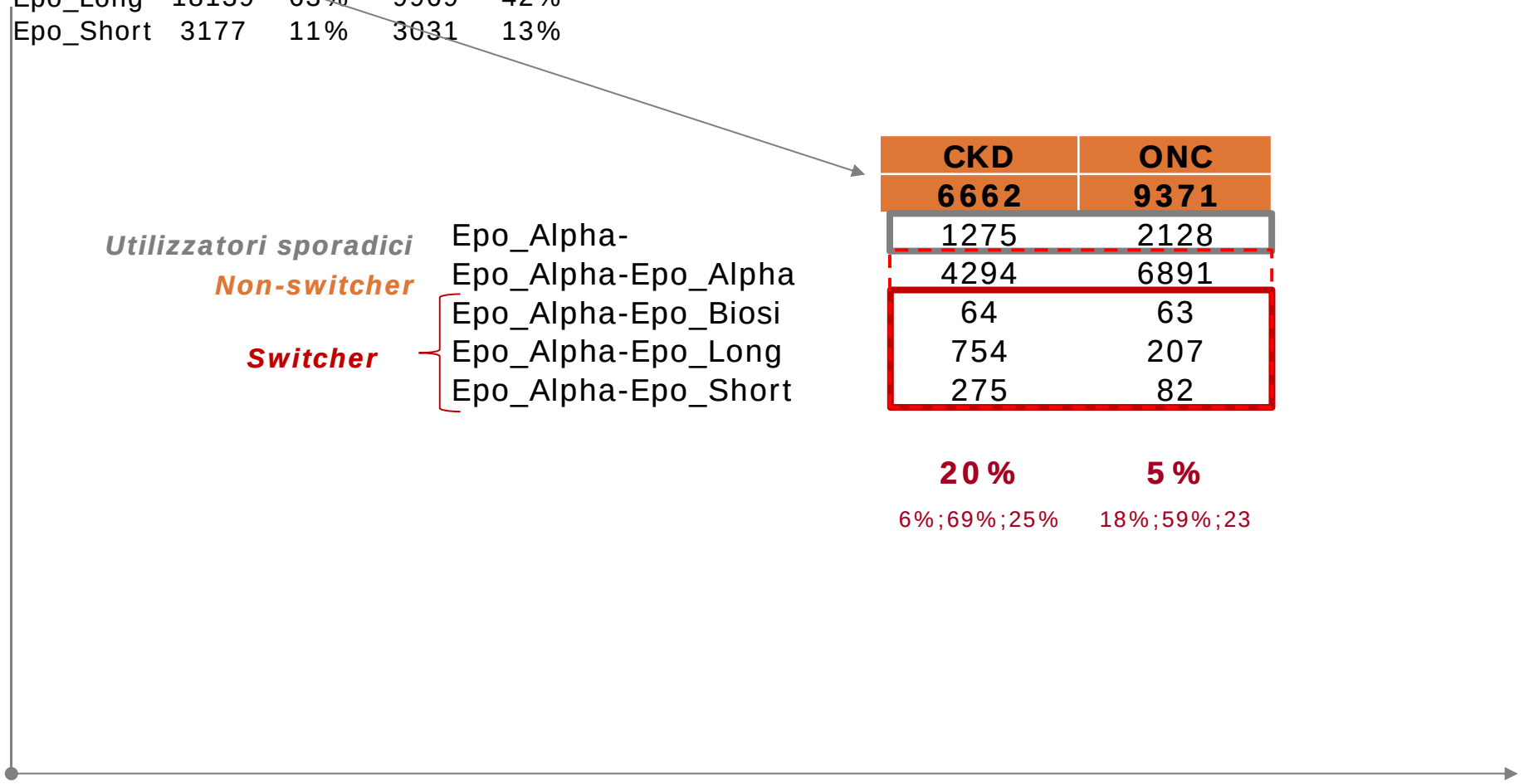
Epo_Short: Eporatio, Neorecormon

		CKD	ONC
		6662	9371
Utilizzatori sporadici	Epo_Alpha-	1275	2128
Non-switcher	Epo_Alpha-Epo_Alpha	4294	6891
Switcher	Epo_Alpha-Epo_Biosi	64	63
	Epo_Alpha-Epo_Long	754	207
	Epo_Alpha-Epo_Short	275	82
		20%	**5%**
		6%;69%;25%	18%;59%;23



Switch: epoetine

	CKD		ONC	
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	Epo_Alpha-Epo_Long	754	207
	Epo_Alpha-Epo_Short	275	82
		20%	5%

		CKD	ONC
		696	1546
Utilizzatori sporadici	Epo_Biosi-	114	240
Non-switcher	Epo_Biosi-Epo_Biosi	472	1217
Switcher	Epo_Biosi-Epo_Alpha	52	55
	Epo_Biosi-Epo_Long	40	12
	Epo_Biosi-Epo_Short	18	22
		19%	7%

		CKD	ONC
		18139	9969
Utilizzatori sporadici	Epo_Long-	2739	2210
Non-switcher	Epo_Long-Epo_Long	14327	7359
Switcher	Epo_Long-Epo_Alpha	631	255
	Epo_Long-Epo_Biosi	102	31
	Epo_Long-Epo_Short	340	114
		7%	5%

		CKD	ONC
		3177	3031
Utilizzatori sporadici	Epo_Short-	612	630
Non-switcher	Epo_Short-Epo_Short	1786	2160
Switcher	Epo_Short-Epo_Alpha	299	121
	Epo_Short-Epo_Biosi	19	27
	Epo_Short-Epo_Long	461	93
		30%	10%

2 years

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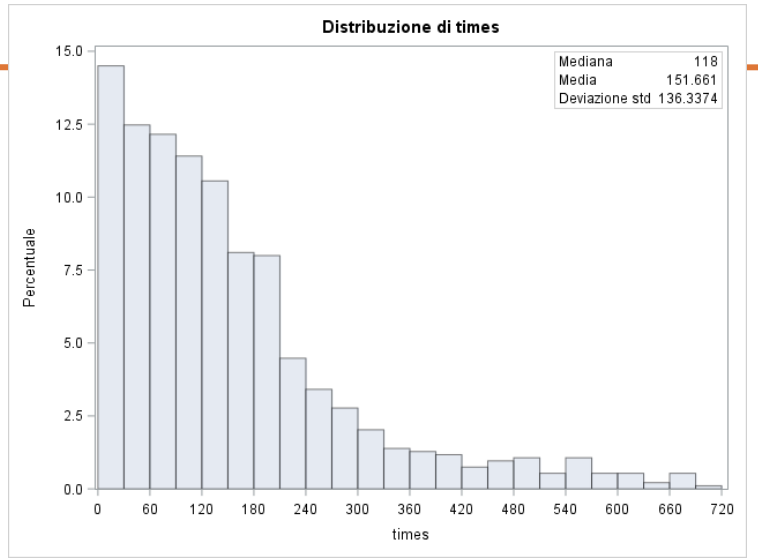
Motivi dello switch

Riuscire ad indagare le ragioni che hanno portato allo switch attravero i sistemi informativi sanitari è complesso:

- inefficacia terapeutica
- scarsa tollerabilità al primo principio attivo
- diminuzione dell'aderenza: problemi legati alla posologia (modalità di somministrazione/dosi)
- motivi organizzativi/economici

Switch: epoetine

Epo_Alpha	CKD
	5387
Non switcher	4294
Switcher	1093
	20%



tempo in trattamento nella terapia indice

match 1:2

Non switcher	1876
Switcher	938

Genere
Età
Anno
Dialisi
Trasfusioni
Reazioni allergiche
Anemia
Ferro
Numero ricoveri pregressi

Tumori
Diabete
Ipertensione
Aritmie
Scompenso
Malattie cerebrovascolari
Vitamine
Ipercalemia

	Non switcher 1876	Switcher 938
INEFFICACIA *anemia/trasfusioni*	4,9%	8,3%
REAZIONI AVVERSE *mace/reazioni allergiche /discrasie*	3,7%	5,5%
PROBLEMI DI ADERENZA *MPR>80%*	46,4%	42,4%

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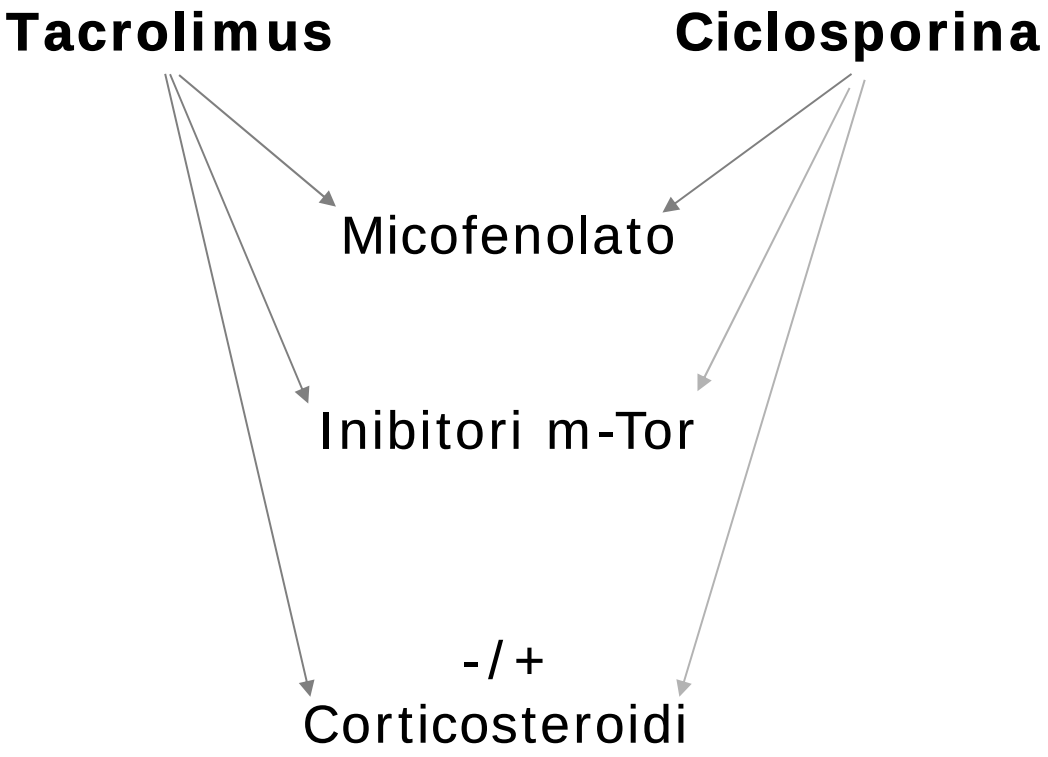
Switch: immunosoppressori

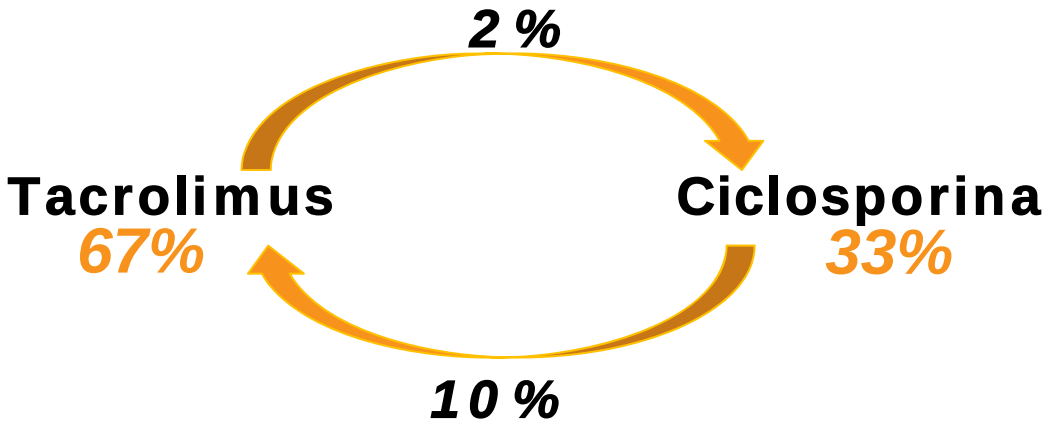
TRAPIANTO DI RENE: terapia di mantenimento

Inibitori della CalciNeurina:



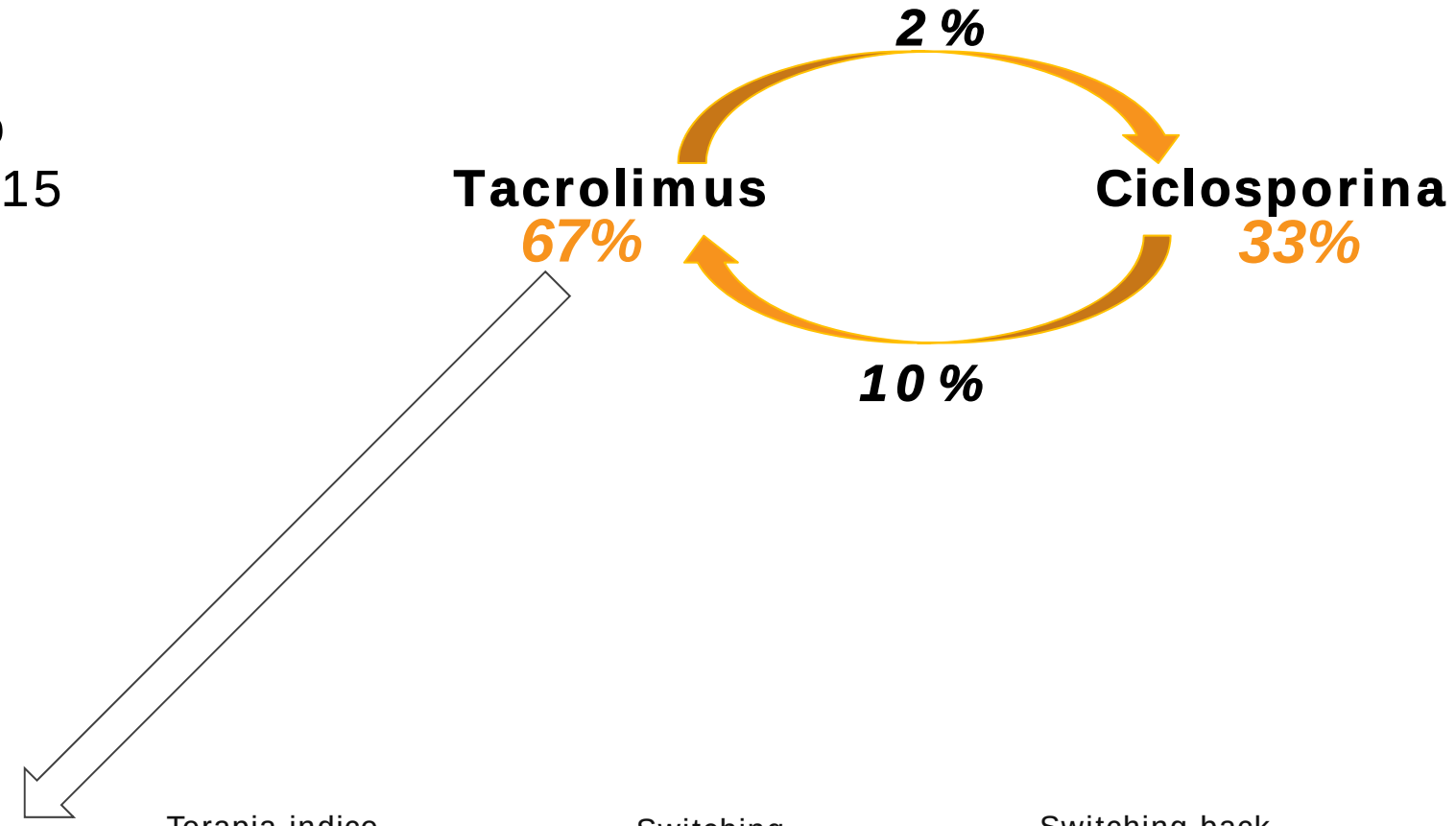
Switch: immunosoppressori

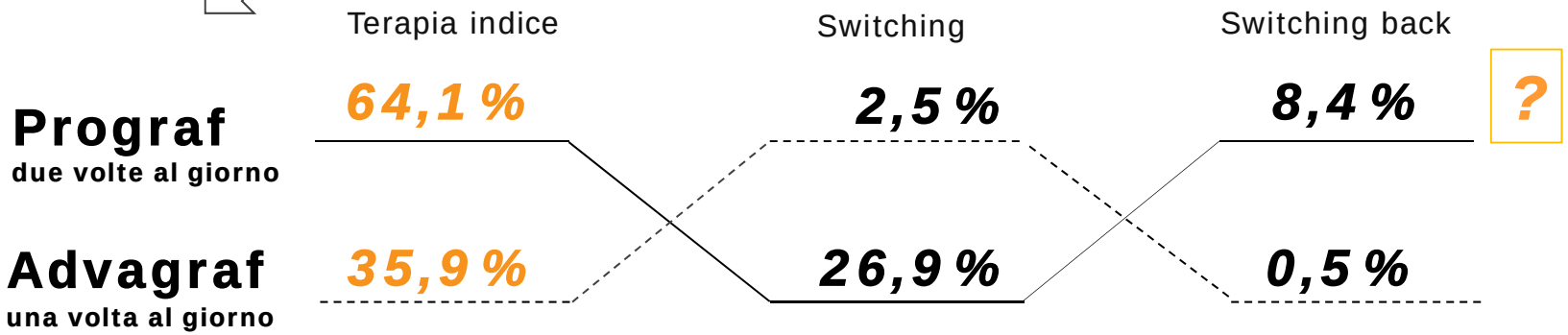
Trapianti
nel Lazio
2006-2015
N=1787



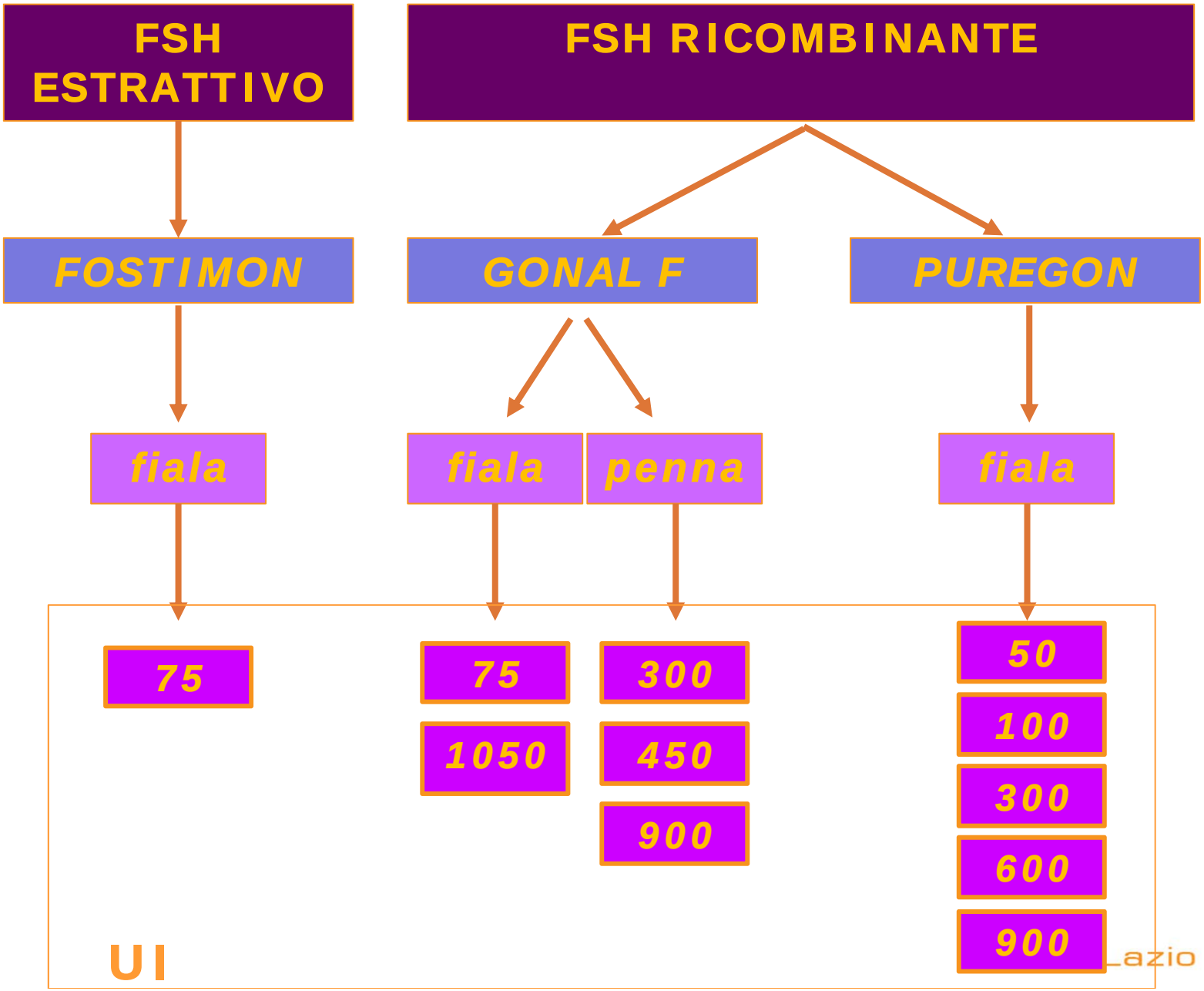
Switch: immunosoppressori

Trapianti
nel Lazio
2006-2015
N=1787

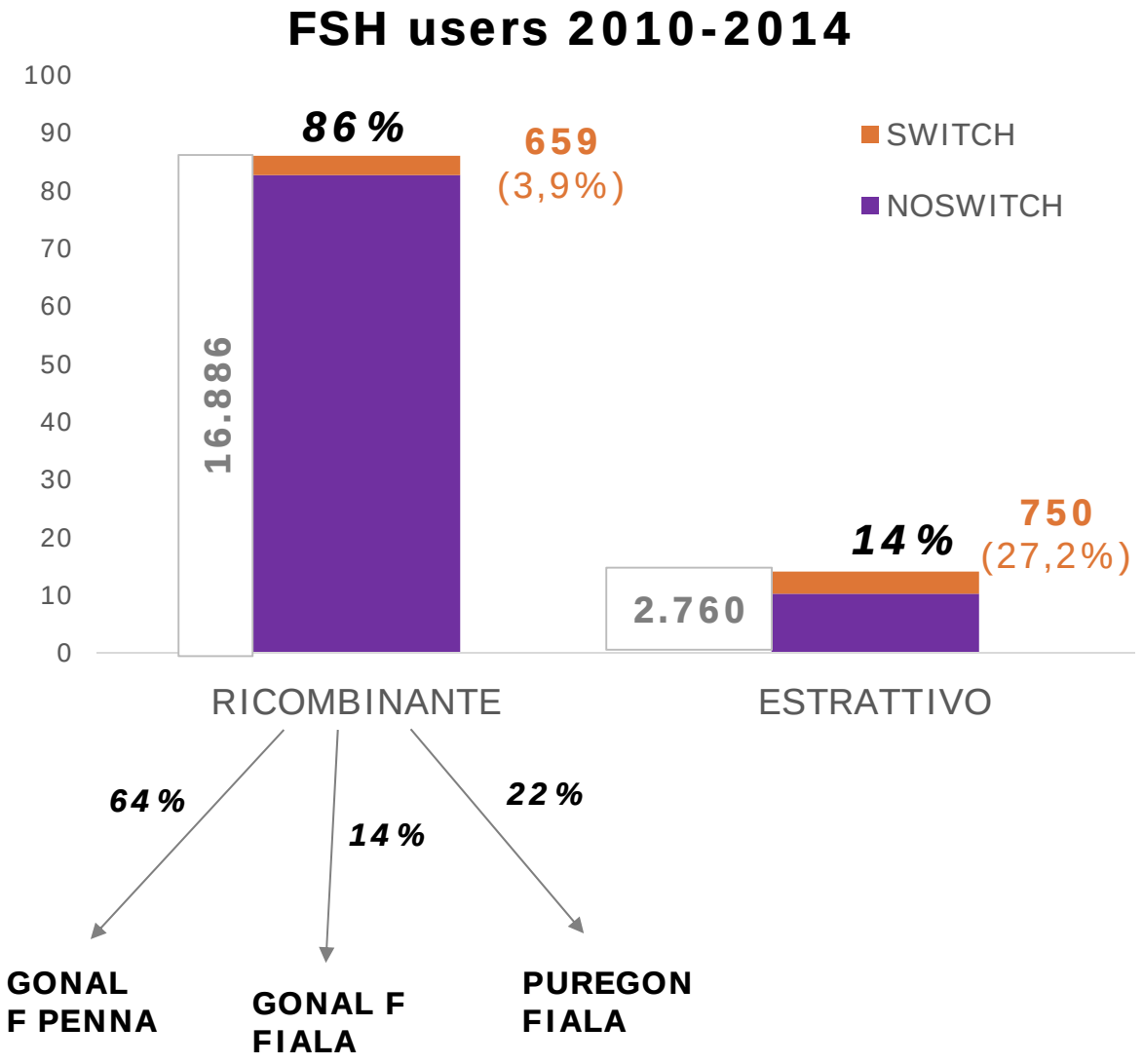




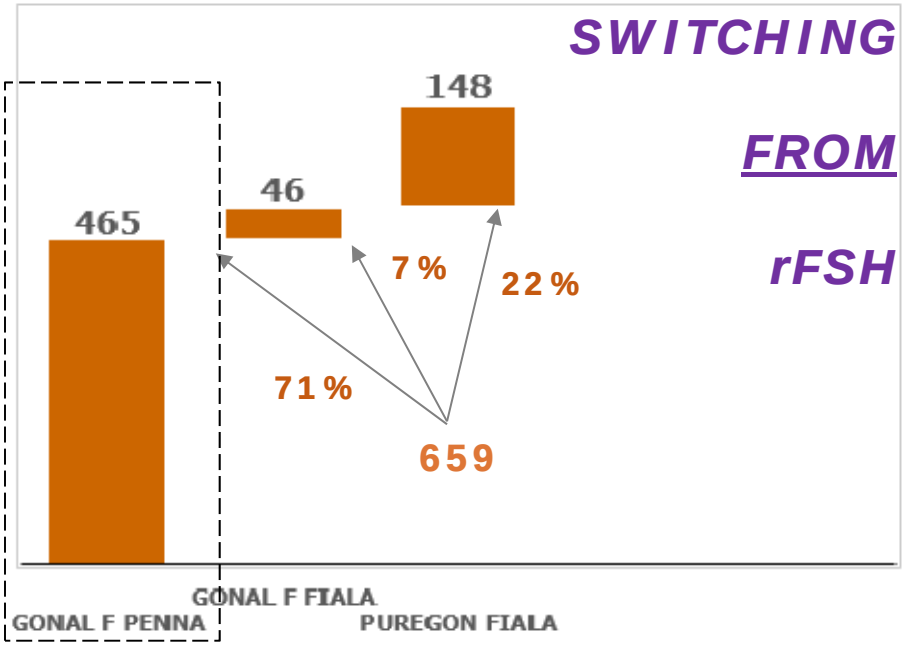
Switch: follitropine

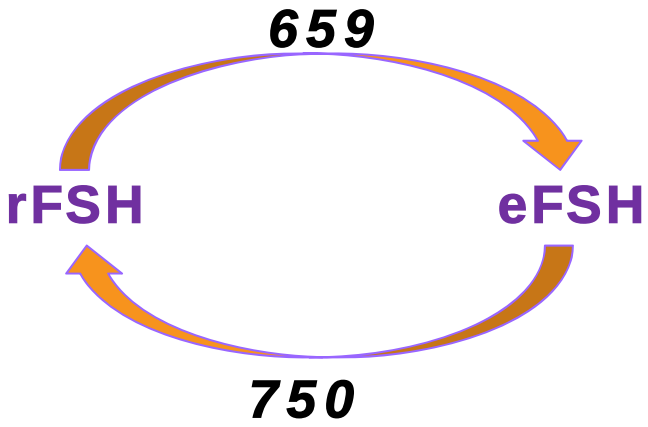


Switch: follitropine



Switch: follitropine

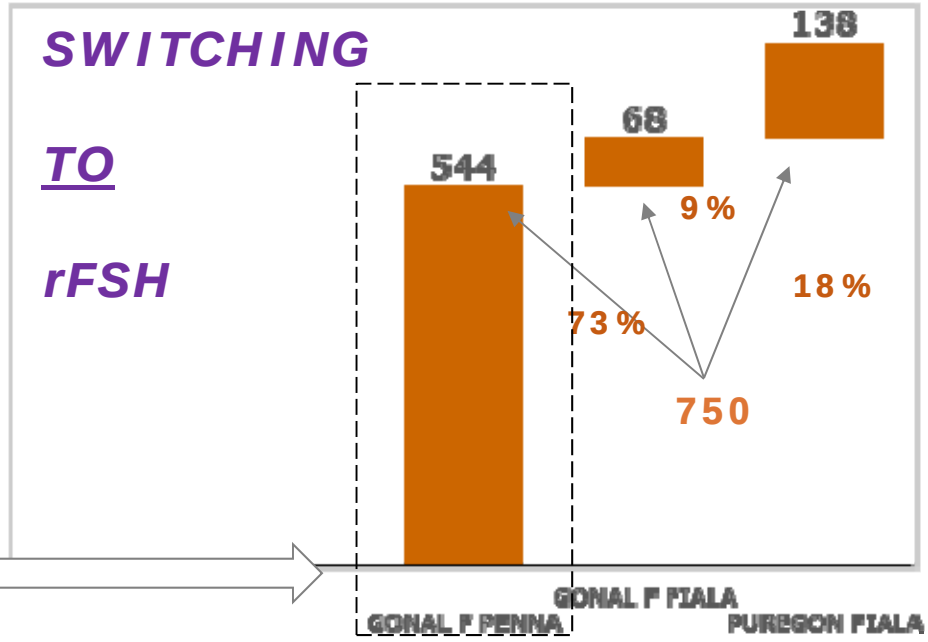




96,8 %

94,9 %

900 UI



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JOURNAL OF MEDICAL INTERNET RESEARCH Risson et al

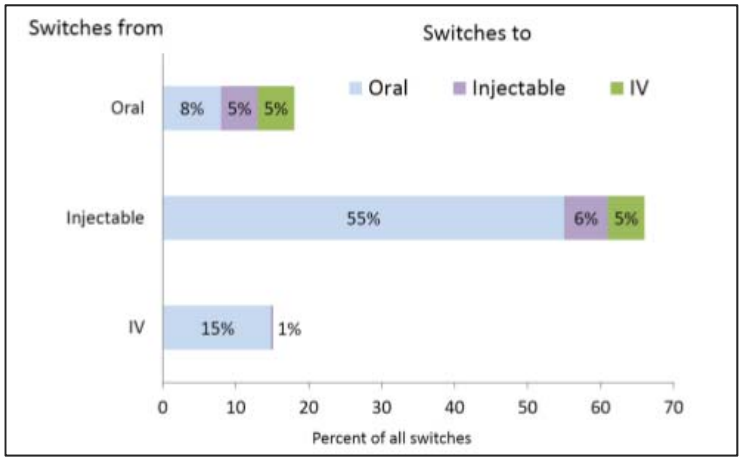
Original Paper (J Med Internet Res 2016;18(3):e62) doi:10.2196/jmir.5409

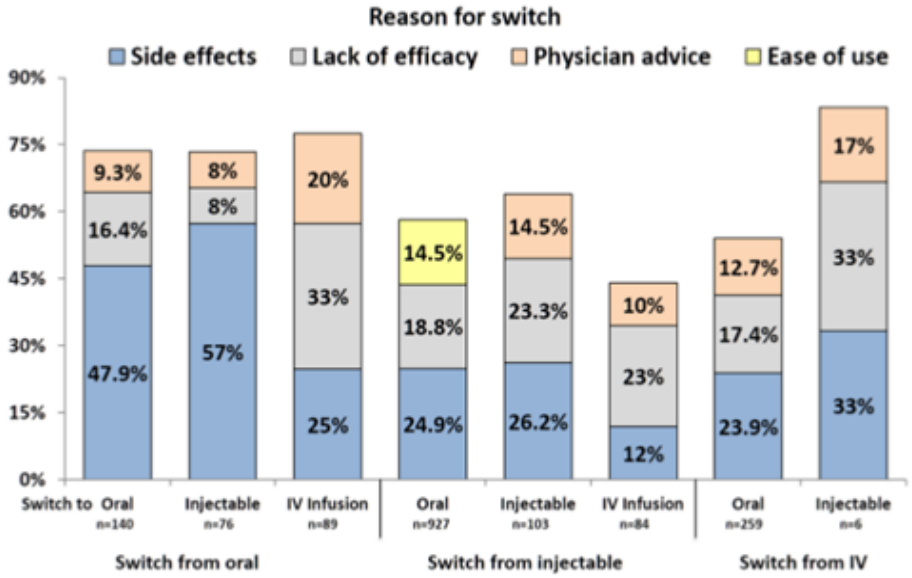
Switch: FUTURO

Patterns of Treatment Switching in Multiple Sclerosis Therapies in US Patients Active on Social Media: Application of Social Media Content Analysis to Health Outcomes Research

Data sources were Facebook, Twitter, blogs, and online forums.

Reason	Frequency, n (%)
Severe side effects of previous drug	464 (37.60)
Lack of efficacy of previous drug	310 (25.12)
Physician's advice	193 (15.64)
Ease of use of new drug	163 (13.21)
Worsening quality of life	39 (3.16)
Safety concerns	38 (3.08)
Insurance issues	13 (1.05)
High cost	7 (0.57)
Other	7 (0.57)





This analysis shows that when applied to appropriate questions that are frequently discussed openly by patients, social intelligence can be a powerful tool for outcomes research, providing information on specific factors driving patient's health-seeking behavior that may not be obtainable by other means.

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Switch e farmacovigilanza: SENTINEL METHODS

Sentinel

SENTINEL METHODS

Methods Development Project: Identify and Evaluate Manufacturer-Level Drug Utilization and Switching Patterns in Sentinel

II. STUDY PURPOSE

The purpose of this developmental methods project is to explore the potential for the Sentinel System[6] and its Sentinel Distributed Database (SDD) to support these types of investigations and to assess their potential for detecting new safety issues related to manufacturer-level switching of the same product.[7,8] As such, this project is intended to address the limitations identified in the prior work in Sentinel, and build upon, contextualize, and extend the extramural work done by OGD.

The Sentinel System could potentially:

- Provide population-based evidence to support equivalence for approved drug products,
- Support identification of potentially problematic drug products for product-specific bioequivalence guidance revision,
- Complement FDA findings on post-marketing bioequivalence studies and internal examinations of formulation or pharmacokinetics/pharmacodynamics when generics are identified as higher risk or non-equivalent,
- Identify potential topics or signals for future investigation (e.g., drugs to evaluate for post-marketing population-based safety and effectiveness studies).

December 12, 2016

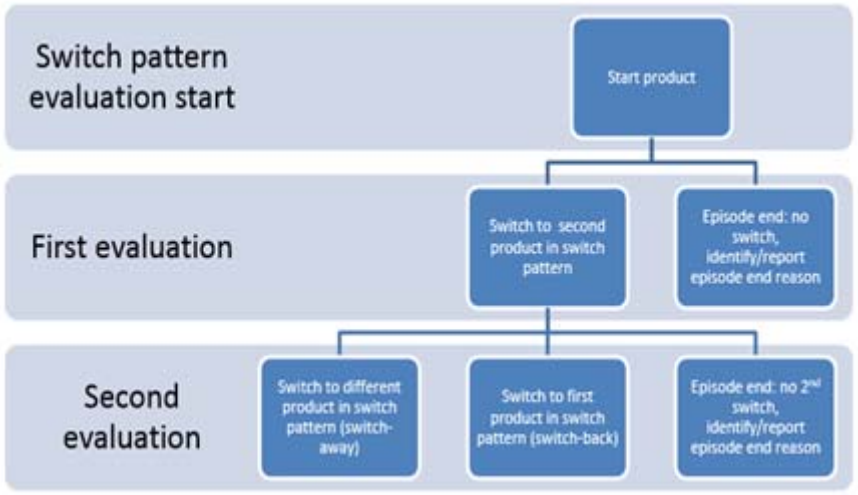
C. ANALYTIC APPROACH

The tool will be flexibly designed in order to facilitate re-use across multiple studies and will leverage existing RAF tools to the extent reasonable, particularly the features, philosophy and analytic approach of the Sentinel Cohort Identification and Descriptive Analysis (CIDA) tool. Cohort identification-related criteria that will be flexibly designed to allow user-defined/specified inputs are listed in Appendix 2. "Switching" will be flexibly defined and could include any switching pattern between products in user-specified product groups. In essence, since outpatient dispensings in the SDD are defined by NDC, any information gleaned from the NDC that could be used to differentiate product characteristics, would be able to be used to capture and characterize product switching. This includes, but may not be limited to:

a) From a brand product to a generic product
b) From a generic product to a brand product
c) From a generic to another generic of the same product (e.g., between different generic versions from different manufacturers within a given drug/active pharmaceutical ingredient [API]), and
d) Switches away to other dosage forms with the same active ingredient or other products within the same drug class.

Drug(s) of interest	# generics	First generic approval date
Toprol XL (metoprolol ER)	6	7/31/2006
Lamictal XR (lamotrigine ER)	7	12/26/2012

Switch e farmacovigilanza: SENTINEL METHODS



Characterizing and **evaluating switching or switchback patterns** may also be used as a **proxy** identifier **of** potential **bioequivalence** issues;

Patient **switching or switchback behavior** may **indicate safety or effectiveness concerns** associated with a specific generic product.

Grant	Institution, PI	Duration	Aims Related to Product Switching
Assessing Clinical Equivalence for Generic Drugs Approved by Innovative Methods *(U01FD004856)*	Brigham and Women's Hospital, PI: Aaron Kesselheim	9/15/2013 to 3/31/2015	Aim #3: identify switchback rates of 6 'model' generic drugs and determine whether the switchback rates differ significantly from switchbacks related to use of 'control' drugs. Then, compare switchback outcomes to patient-centered outcomes [outcomes were disease specific (AE-related) hospitalizations]. Database: Optum LifeSciences Research Database
Postmarketing Surveillance of Generic Drug Usage and Substitution Patterns *(U01FD004855)*	University of Maryland Baltimore/IMPAQ International, PI: Ilene Harris	9/15/2013 to 10/31/2015	Aim 2: Estimate brand and generic drug use and switchback rates, and investigate medical service use associated with generic switching Database: CMS Medicare claims, 5% random sample
Assessing the post-marketing safety of authorized generic drug products *(1U01FD005279)*	Brigham & Women's Hospital, PI: Joshua Gagne	9/10/2014-8/31/2016	Aim 1: Compare substitution and switchback rates, adherence, medical utilization, and clinical outcomes between authorized generic and other generic versions of model drug products and between other generic versions and brand versions of these drugs Databases (5): PA and NJ Medicare data + pharmaceutical assistance programs dispensing data; national Medicaid Analytic Extract (MAX); Optum Life Sciences Research database; Aetna + CVS CareMark; Medicare enrollment, A, B + CVS CareMark data
Post-market Authorized Generic Evaluation (PAGE) *(1U01FD005272)*	Auburn University, PI: Richard Hansen	9/10/2014-8/31/2016	Aim 1: To determine and compare switchback rates, medical service utilization, and clinical outcomes between authorized generics and generics using healthcare claim data with electronic medical records. Database: Marshfield Clinic Electronic Health Record (EHR) + Security Health Plan (SHP)

Switch e farmacovigilanza: SENTINEL METHODS

Table 7: Summary statistics for time to first switch in days (of initiators of a start product of interest), by SwitchPattern and stratified by switched or episode end (and by reason for episode end). *One table for each site and one for all sites aggregated.*

	All	Switched	Episode end (reason for end)				
			End query period	End enrollment	End available data	Product discontinuation	Death
SwitchPatternA							
Minimum							
Maximum							
Mean							
25th percentile							
Median							
75th percentile							
Total time, in days							
Number of episodes							
Number of patients							
SwitchPatternB							
Minimum							
Maximum							
Mean							
25th percentile							
Median							
75th percentile							
Total time, in days							

Table 9: Switch pattern episode duration summary statistics, by switch pattern and site

	Number of patients	Minimum	Maximum	Mean	25th percentile	Median	75th percentile
SwitchPatternA							
Site 1							
Site 2							
Site 3							
Site 4							
SwitchPatternB							
Site 1							
Site 2							
Site 3							
Site 4							

Table 10: Frequency distribution of patients who switch, by number of months to first-switch. One table for each switch pattern (at least one switch pattern). *One table for each site and one for all sites aggregated.*

Months	Number and percent (of patients with at least one switch pattern)
1	
2	
…	
x	

Table 11: Frequency distribution of patients who switch, by number of months to second-switch. One table for each switch pattern (two-switch patterns only). *One table for each site and one for all sites aggregated.*

Months	Number and percent (of patients with two-switch pattern)
1	
2	
…	
x	

Table 12: Number of months for X percent of patient to switch (at least one-switch pattern). X percent TBD (e.g., 10%, 25%, 50%, 75%, etc.). *One table for each site and one for all sites aggregated.*

Percentile	Number of months from initial product index to first switch
10	
25	
50	
75	
100	

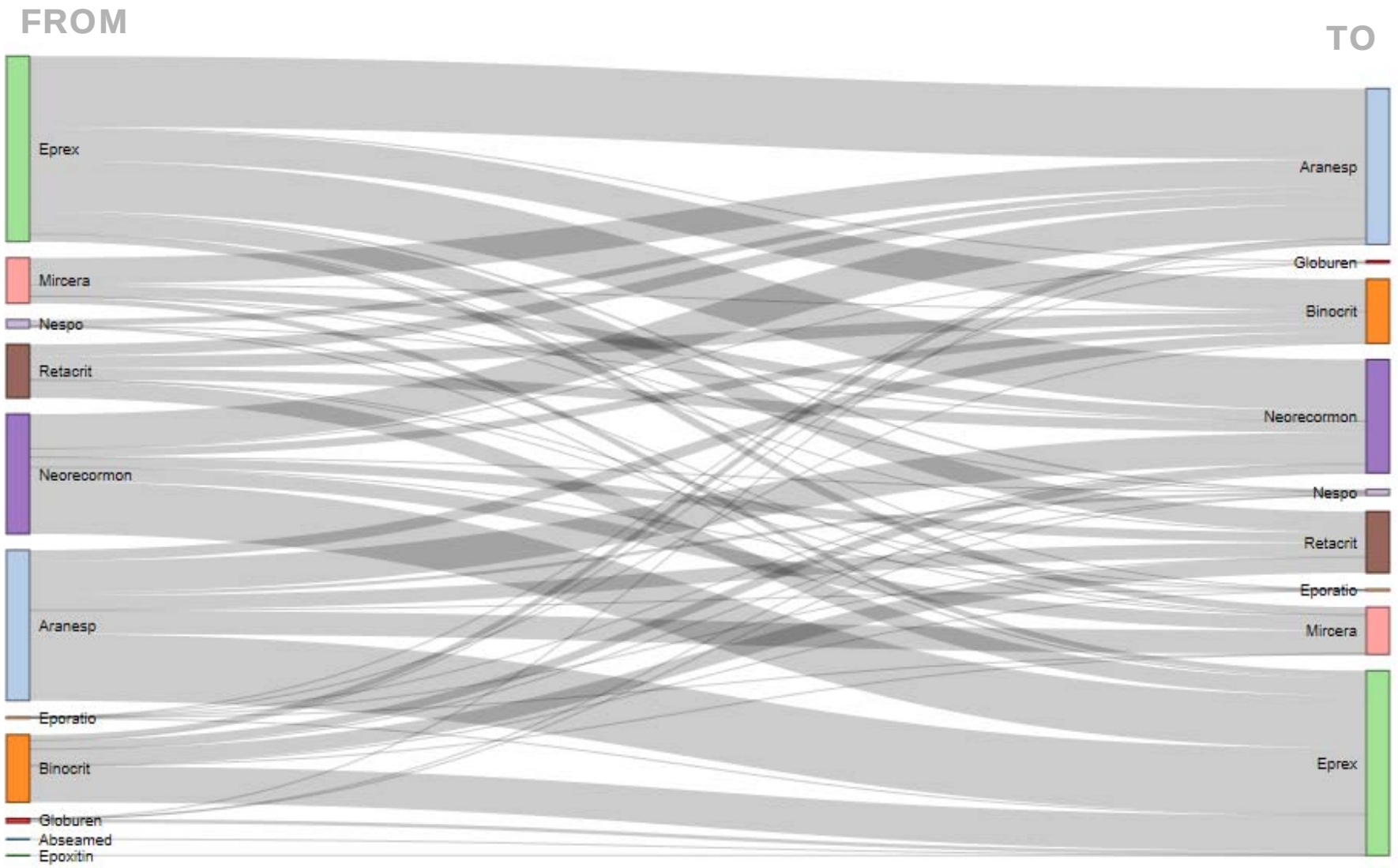
Table 13: Number of months for X percent of patient to switch-back or switch-away (two-switch pattern only). X percent TBD (e.g., 10%, 25%, 50%, 75%, etc.).

Percentile	Number of months from first switch product index to second switch

Table 14: Time to first switch, in days, from user-specified index date

	Min	Max	Mean	25th percentile	Median	75th percentile	Total time, in days	Number of episodes with at least one-switch pattern	Number of patients with at least one-switch pattern
SwitchPatternA									
Site1									
Site2									
Site3									
Site4									
SwitchPatternB									
Site1									
Site2									
Site3									
Site4									

Switch: sankey diagram



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