Assisted Reproductive Technologies – From activity to regulation or vice-versa?

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ART – From activity to regulation or vice versa ?

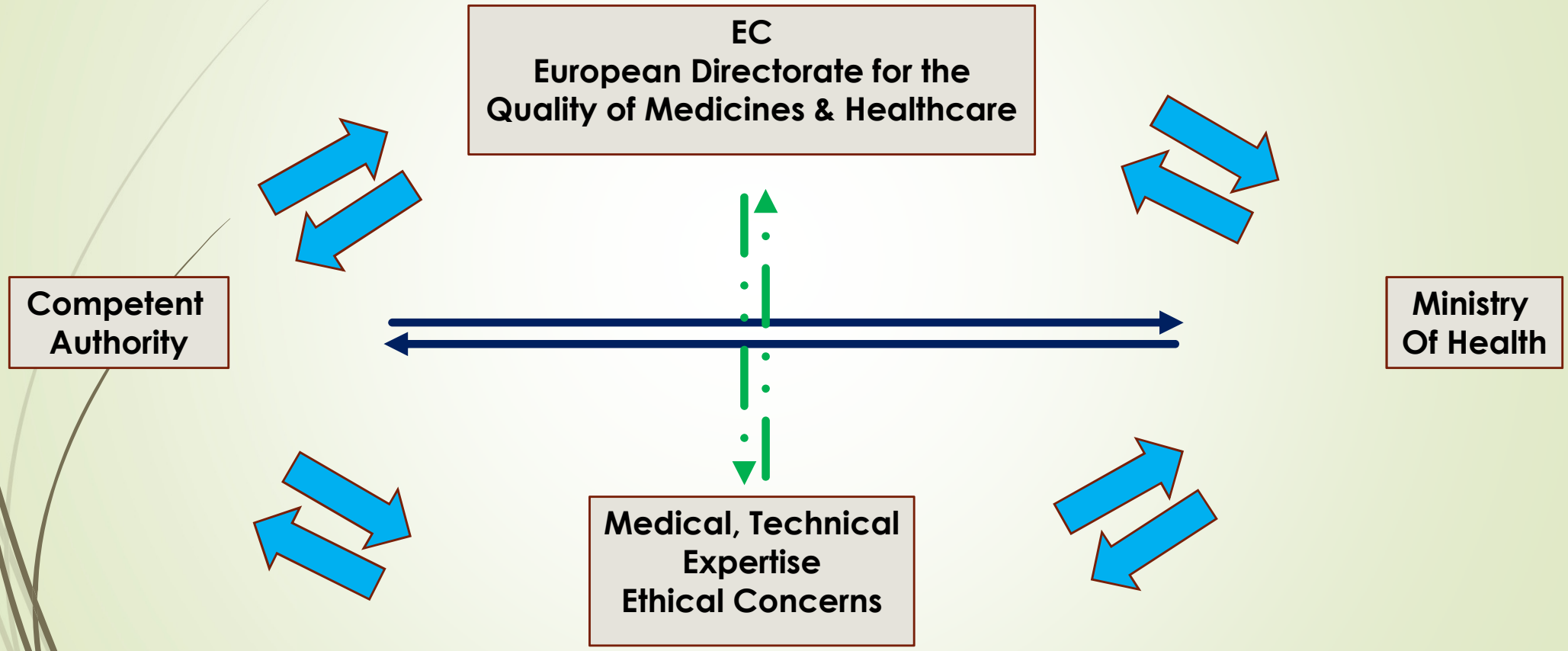
- **ART – From activity to regulation and vice versa = conclusion**

- **Objectives**
  - **Why ART activities need regulation?**
  - **How ART activities may be regulated? The need of a dialog between professionals and authorities to ensure quality, safety and efficiency in ART activities**
  - **Several examples illustrating the positive impact of such a dialog.**

ART – the need for a regulation

- Rapid development of ART activities for 40 years
- High national variability in the legal framework
- EUTCD 2004/23, followed by Technical Directives 2006 2015 aimed to develop a high level of quality and safety for human tissues and cells intended for clinical use, including Reproductive tissues and cells
- Although these directives were transposed and theoretically implemented by all EU MS, ART practice and legislation vary considerably within and between the MS.
- Two days meeting : huge differences regarding the access to ART, concerning indication, gamete donation, preimplantation genetic diagnosis, self preservation of gametes, including, as mentioned the day before, cross reproductive care.
- The common denominator remains for patients, health care providers, services and Competent Authorities to ensure safety, quality and efficiency in these activities with an equal access for all patients.

ART – How ART activities may be regulated?



First example : Air quality in the IVF lab & the EUTCD 2004/23 & Technical Directives 2006/86

- COMMISSION DIRECTIVE 2006/86/EC of 24 October 2006
  - …"*The air quality standard during the processing of tissues and cells is a key factor that may influence the risk of tissue or cell contamination. An air quality with particle counts and microbial colony counts equivalent to those of Grade A, as defined in the European Guide to Good Manufacturing Practice, Annex 1 and Commission Directive 2003/94/EC (2), is generally required. However, in certain situations, an air quality with particle counts and microbial colony counts equivalent to those of Grade A standard is not indicated. In these circumstances it should be demonstrated and documented that the chosen environment achieves the quality and safety required for the type of tissue and cells, process and human application concerned*."
- European Directive initially stemmed from pharmaceutical standards and cell therapy, which is quite inappropriate for IVF
  - Gametes and embryos
    - are extremely sensitive to physical , chemical stress,
    - require strict temperature, osmolarity and pH control, as well as an absence of chemical contamination during manipulation and culture
  - Grade A almost impossible to obtain in IVF conditions (turbulences and backwash)
  - Laminar flow cabinet (switched on) highly incompatible with ICSI practice
  - Whereas air quality in the close environment is critical (class D or ISO 8) with a special attention for VOC

First example : Air quality in the IVF lab
ESHRE Guideline Group on good practice in IVF labs December 2015

- 3.2 Laboratory air quality
  - 3.2.1 To optimise environmental conditions, laboratory air should be subjected to high-efficiency particulate air (HEPA) and VOC control.
  - 3.2.2 Positive pressure is recommended to minimise air contamination.
  - 3.2.3 Procedures involving gamete or embryo manipulation should be performed in a controlled environment. Background and processing air quality should comply with European and national guidelines, and should be regularly monitored.
  - 3.2.4 According to the European Union Tissues and Cells Directive (EUTCD), tissue and cell processing must be performed in a Good Manufacturing Practice (GMP) Grade A environment with a background of at least GMP Grade D. However, if it is detrimental or not feasible to carry out a specific procedure in a Grade A environment, it can be performed in at least a Grade D environment.

Next example : INSTITUTIONAL GUIDELINES FOR ART COMPETENT AUTHORITIES

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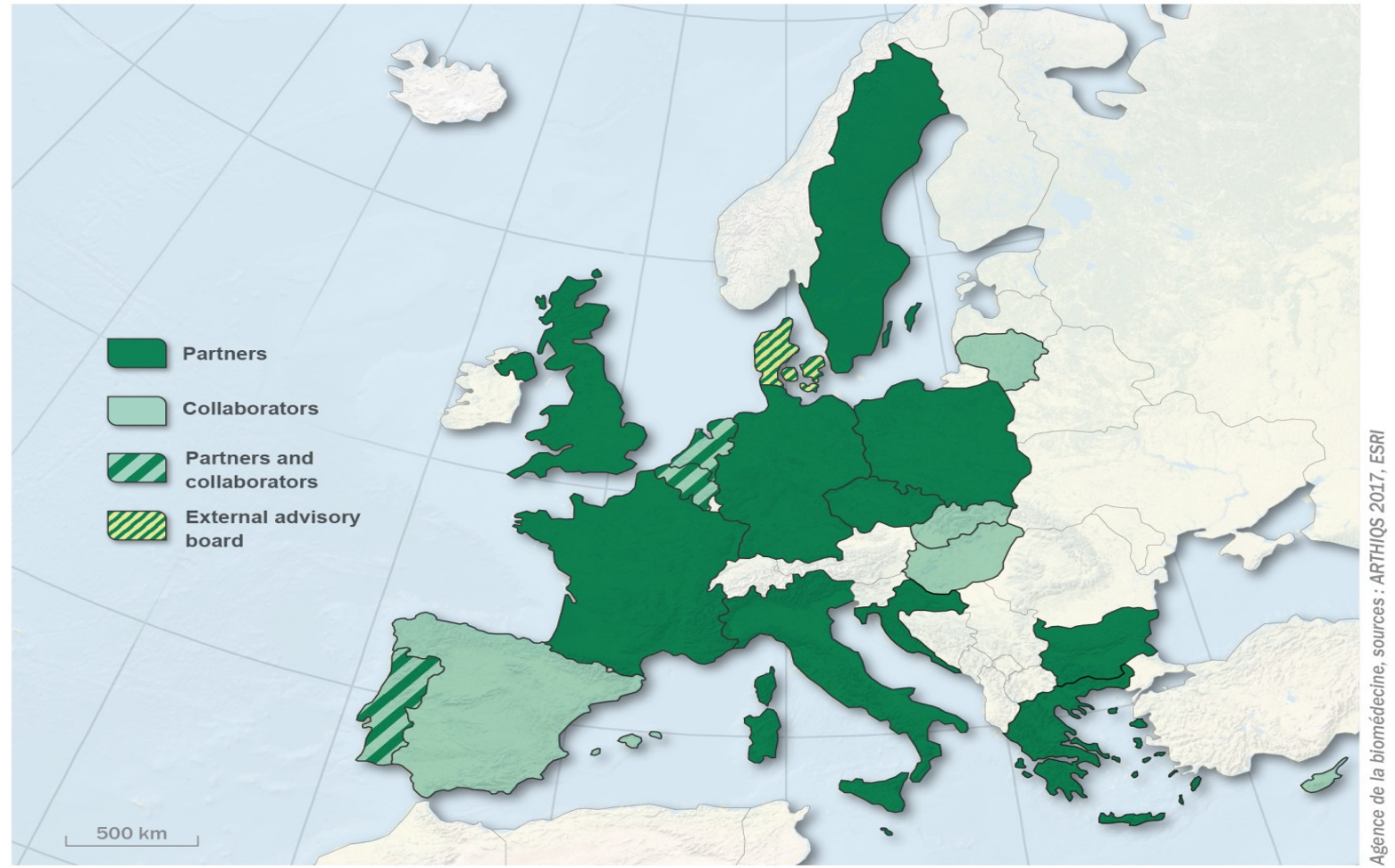

ARTHIQS is a 3 year European Joint Action funded by the European Commission under the 2008-13 Health Programme, dealing with Assisted Reproductive Technologies and Haematopoietic Stem cells for transplantations. ARTHIQS consortium brings together 16 partners and 9 collaborators from 18 different Member States.

Disclaimer

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1. Authorisations/Licensing…
2. Inspections
3. Traceability
4. Vigilance and surveillance
5. Data collection and management, evaluation and follow-up
6. Communication
7. Guidance
8. Ethical overview

These institutional guidelines were developed by Work Package 4, led by the French ART Competent Authority the Agence de la biomédecine, who is also the project coordinator. The plan of the document and the scope of the guidelines were decided collegially during the Lisbon meeting in June 2015. The content was largely developed and explored through a series of workshops during the Prague meeting in October 2016

4 - ART Vigilance and Surveillance

- Develop an ART vigilance and surveillance system through specific skills, monitoring and reporting systems
- Ensure collaboration with other authorities when appropriate
- Raise alert at the national and EU (RATC) level when appropriate
- Ensure that SARE in cross border context are managed
- Report annually to EC

Vigilance aims to improve quality and safety in ART practices and learn from encountered difficulties or mistakes. Health care providers must understand that the notification of SARE does not necessarily lead to inspection, administrative sanctions or penalties except where public health is seriously endangered or in cases of illegal and fraudulent activities

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- Consider the specificities of ART
  - SARE, from initial ovarian stimulation to the follow-up of the children's health, can affect the health of beneficiaries, donors or offspring irrespectively of the quality and safety of the reproductive T&C themselves
  - SARE are mostly associated with the loss of gametes and embryos and the subsequent lost chance of pregnancy, rather than transmission of disease or treatment failure
- Monitor the efficacy of the corrective measures applied at the local level ; help ARTE to investigate the SARE, analyse root causes and take appropriate corrective measures
- Communicate and implement corrective measures at national level ; propose guidelines if appropriate
- Organise coordination between ART Vigilance Systems and other vigilance systems (e.g. Pharmacovigilance, MD Vigilance)
- Trigger a rapid alert when a SARE could have immediate direct or indirect consequences in another country

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How to handle a new and sudden threat such as an emergent infectious disease?

The French experience (ABM)- January 2018 Update

- *The large scale epidemic of Zika that emerged in South America at the end of 2015 led the Agence de la biomédecine to publish guidelines for reproductive health professionals in January 2016. Zika is thought to have serious consequences on foetal health and the initial guidelines aimed to limit public health risks in France and in the French overseas territories (Martinique, Guadeloupe and Guyana) in a very uncertain situation.*
- *Along with development on Zika knowledge, recommendations have since been revised four times following the consultation of domain experts (in ART in viral context, the Agence française de la santé publique (the French public health agency), the Arbovirus reference centre and the Haut Conseil de Santé Publique (the French public health advisory board)). The current version integrates the latest scientific findings and is consistent with international guidelines.*
- *All of the ART Competent Authority's services were involved: in developing and disseminating these guidelines, in communicating with professionals and the general public, in evaluating actions, and in authorisation, inspection and vigilance activities.*
- *The lessons learned from the Zika epidemic will help France to establish processes that National public Authorities can use to identify the actions they must take when new infectious risks emerge.*

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Preventing disease transmission in non partner gamete donation

- As an example, in one of the best known cases of donor transmitted genetic conditions, sperm donated from a single donor (Danish sperm donor 7042) between 2004 and 2009 was distributed worldwide transmitting neurofibromatosis to five of the 43 children it was used to conceive before the mutations and the risk was identified and distribution interrupted. This led to the revision of Danish law and sperm donation practices specifically limiting the number of children that can be conceived using a single donor's sperm.
- *Clinical presentations of 23 half-siblings from a mosaic neurofibromatosis type 1 sperm donor.* Clin Genet *(2016) Ejerskov C* et al. *89(3):346-50*

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Preventing disease transmission in non partner gamete donation

- However,
- **Direct distribution**
  - Nowadays individuals can purchase non-partner donor sperm directly through the Internet and receive them at home by post for private use. The practice is not allowed in all member states, traceability and vigilance cannot be ensured and clinical application is performed without any medical expertise. This leads to antagonism between certain gamete providing tissue banks and certain member states.

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5 -Data collection and management, evaluation and follow-up

- Ensure data collection, monitoring and evaluation of ART activities from ARTEs.
- Establish and maintain a national register including offspring and non-partner donation follow-up
- Evaluate quality, safety and efficacy with the different ART processes, with the aim to improve and harmonise practices
- Ensure data security measures, while a publicly accessible register of authorised ARTEs is also in place
- Publish an annual report of ART activities and performance

Some of these actions do not necessarily have to be carried out by the CA itself but can be delegated to professional bodies or health research public organisations

Legal expertise could be necessary to take into account obligations regarding sensitive data according to GDPR

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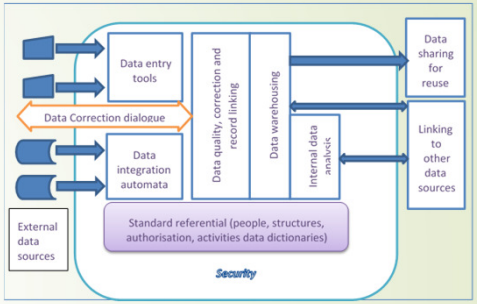
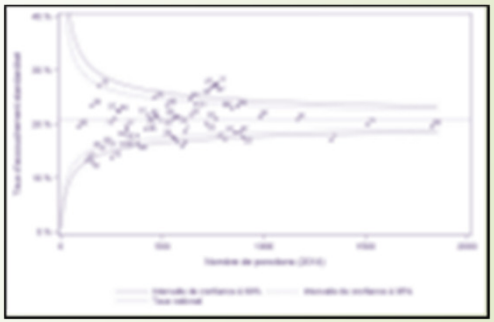
- Data collection
- Processing system architectures
- Data protection and confidentiality in particular as regards risks of disclosure of recipients and donors' identities
- Reuse of data
- Evaluation of routine ART and new processes
- Participate in Eurocet data collection
- Evaluation of ART results
- Follow-up of children and women's health
- Registration of non-partner donors and donations





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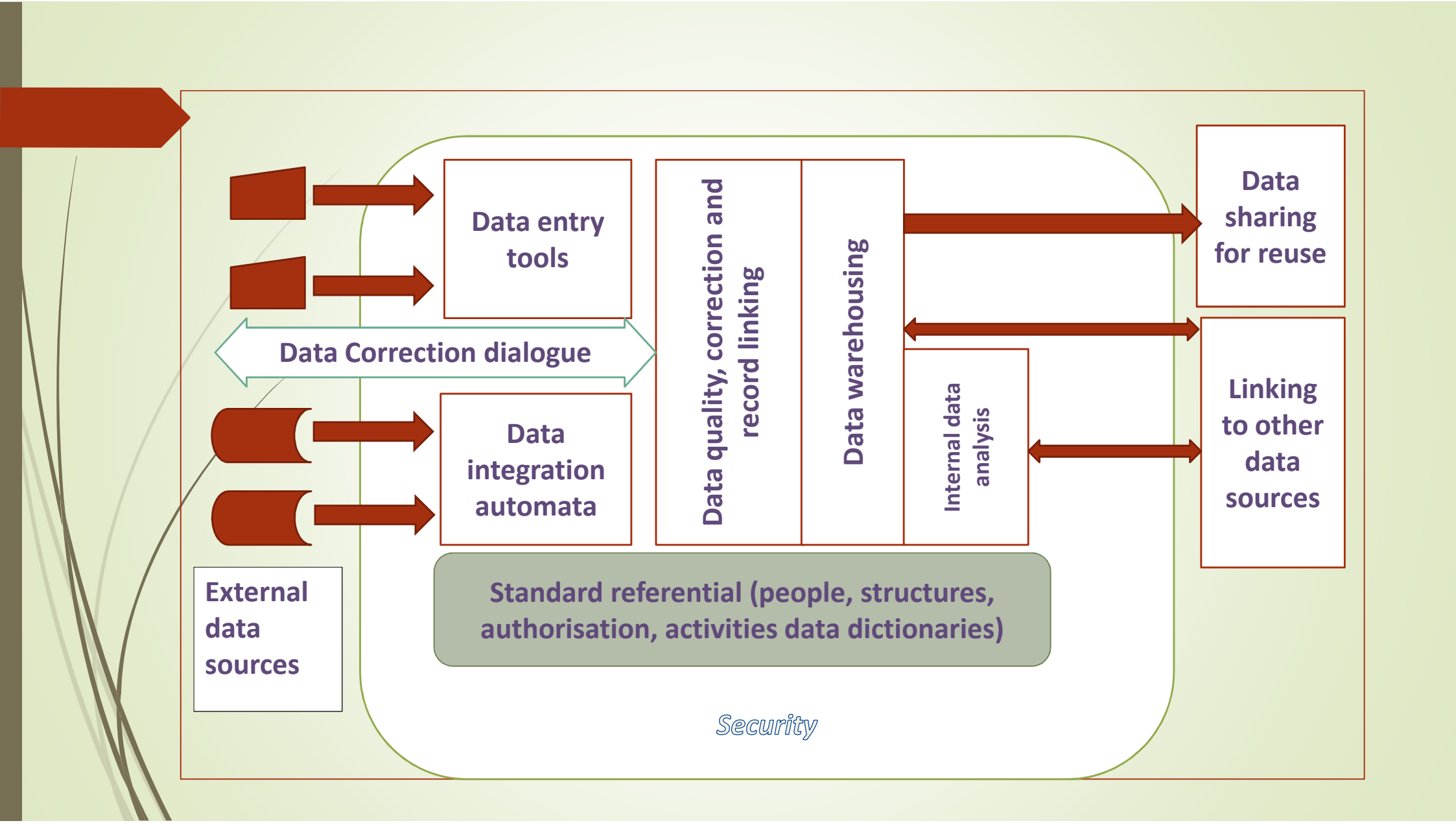
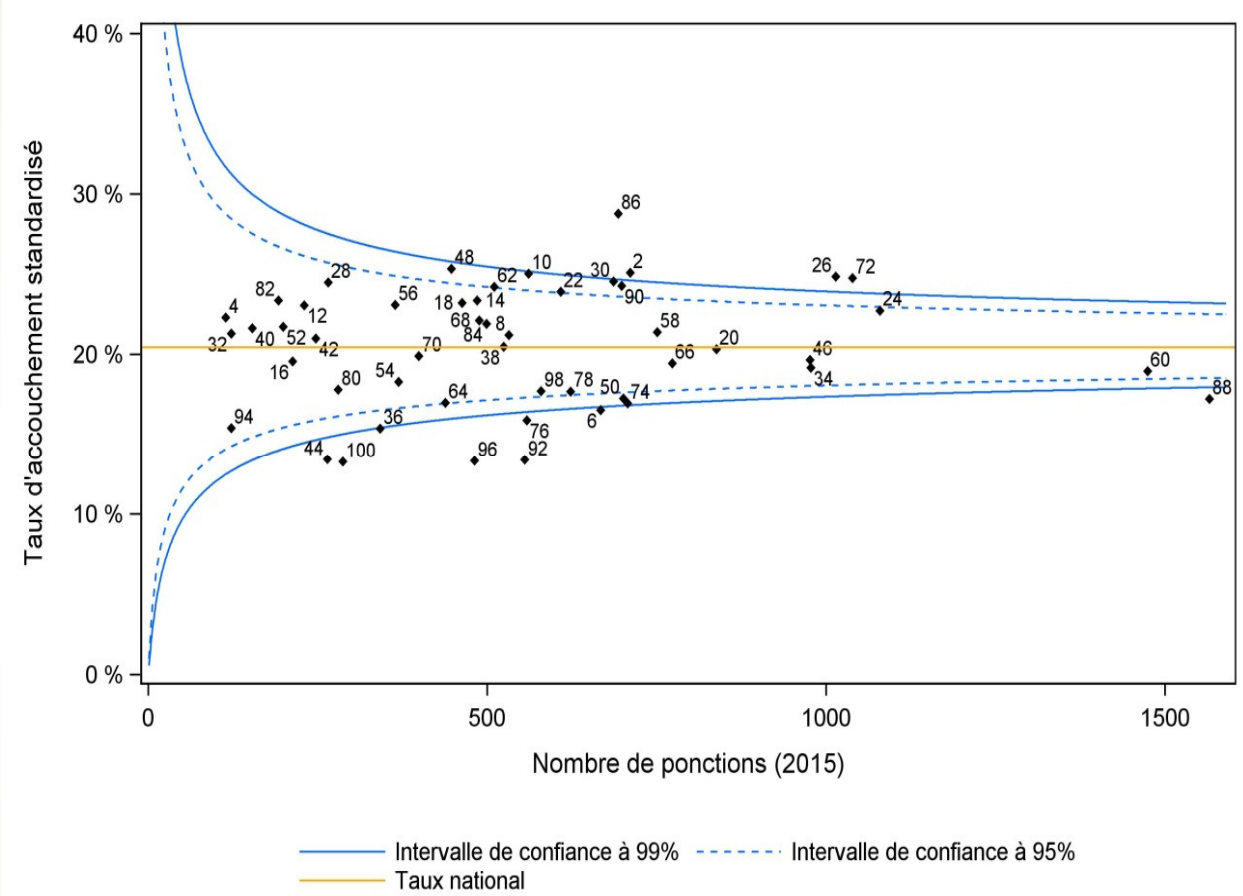

Data entry tools
Data Correction dialogue
Data integration automata
External data sources
Data quality, correction and record linking
Data warehousing
Internal data analysis
Standard referential (people, structures, authorisation, activities data dictionaries)
Security
Data sharing for reuse
Linking to other data sources

Standardised cumulative LBR issued from fresh embryo transfers for the oocytes recoveries in 2015 : statistical evaluation by comparison to the national mean using « Funnel plot methodology »



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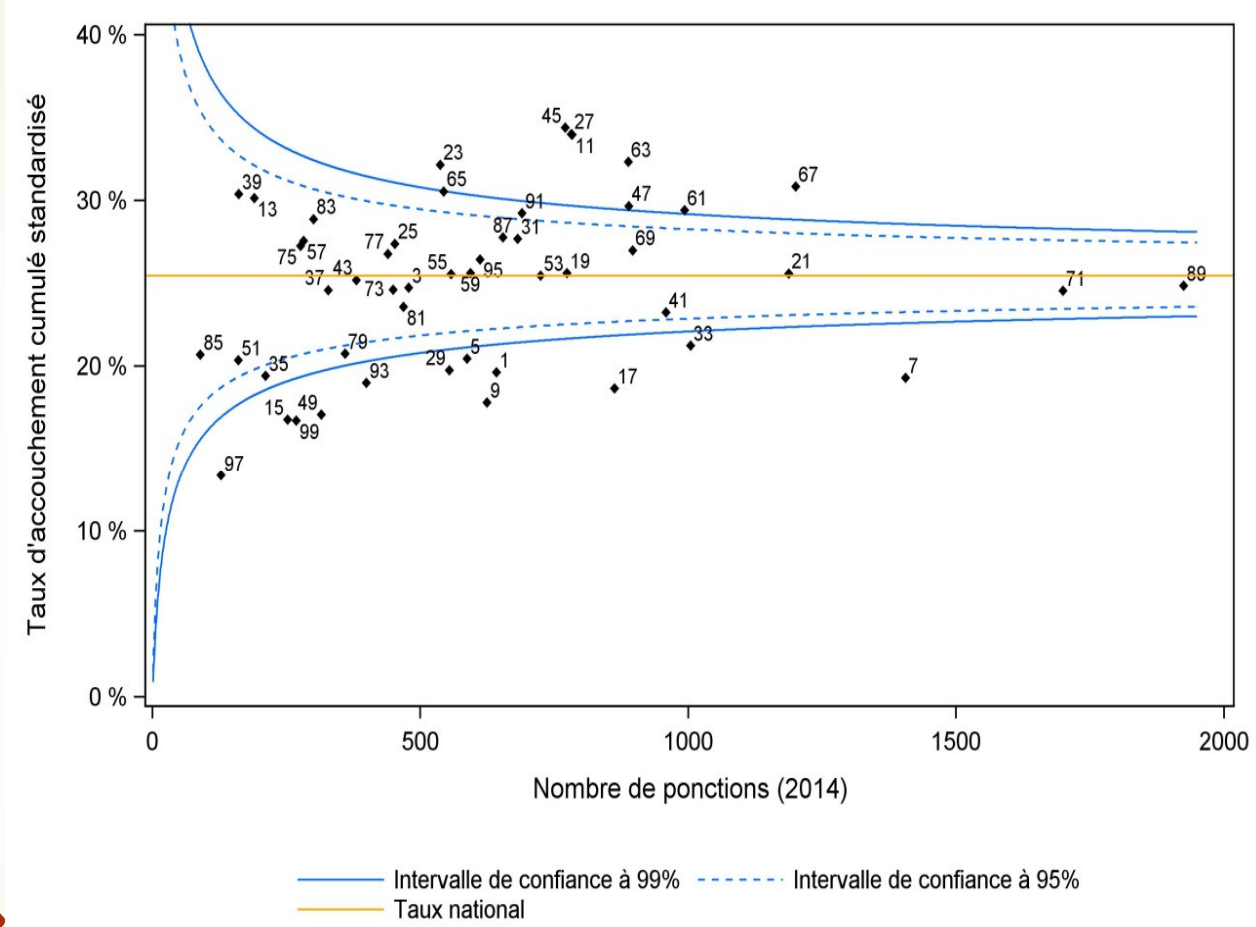
Standardised cumulative LBR issued from fresh & frozen embryo transfers (2014, 2015) for the oocytes recoveries in 2014 : statistical evaluation by comparison to the national mean using « Funnel plot methodology »



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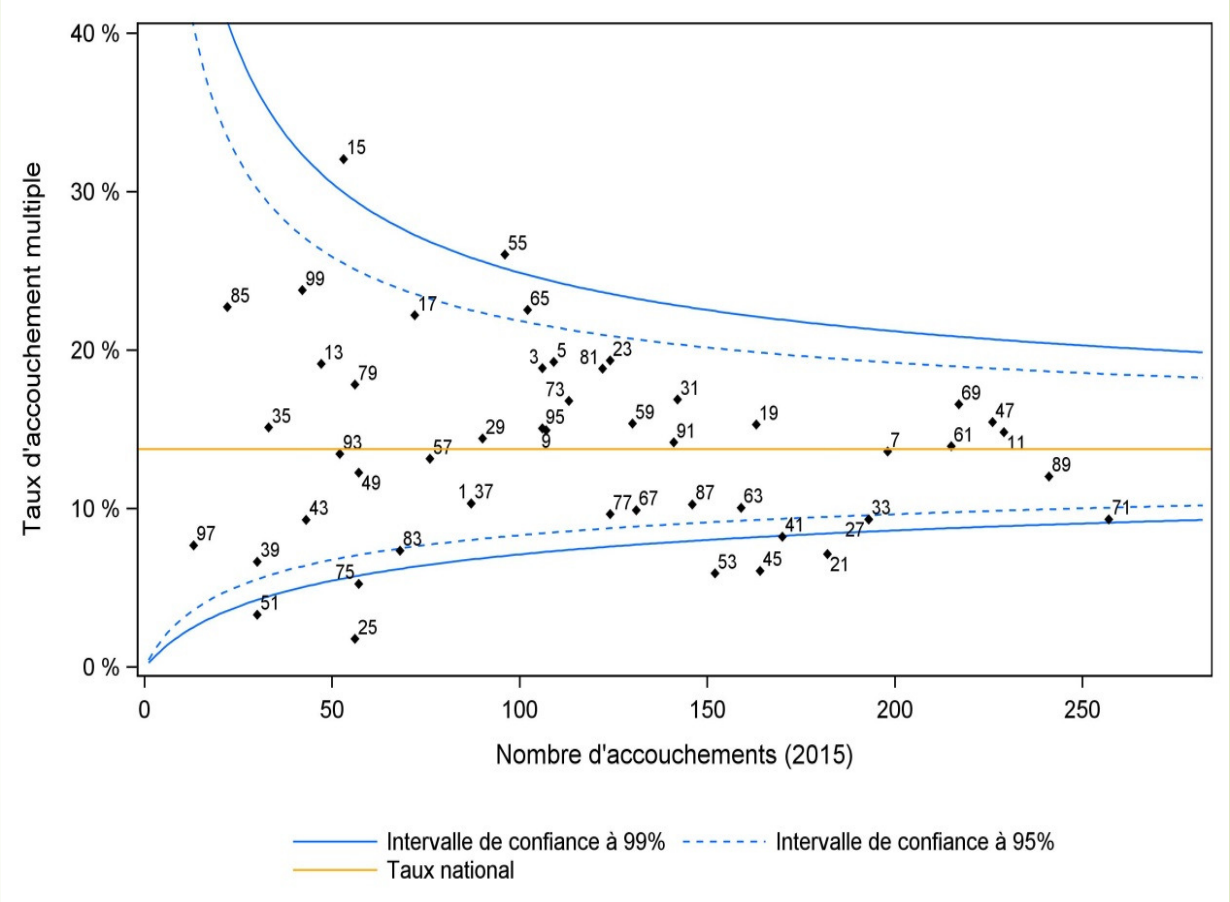
Multiple delivery Rate in 2015 : statistical evaluation by comparison to the national mean using « Funnel plot methodology »



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Tabular CUSUM methodology

Pregnancy rate follow up in « real time »

Indicator :

- Cumulative sum of differences to a reference (O-E)

Graphic representation :

- Evolution tendency
- Statistical test: comparison to the reference

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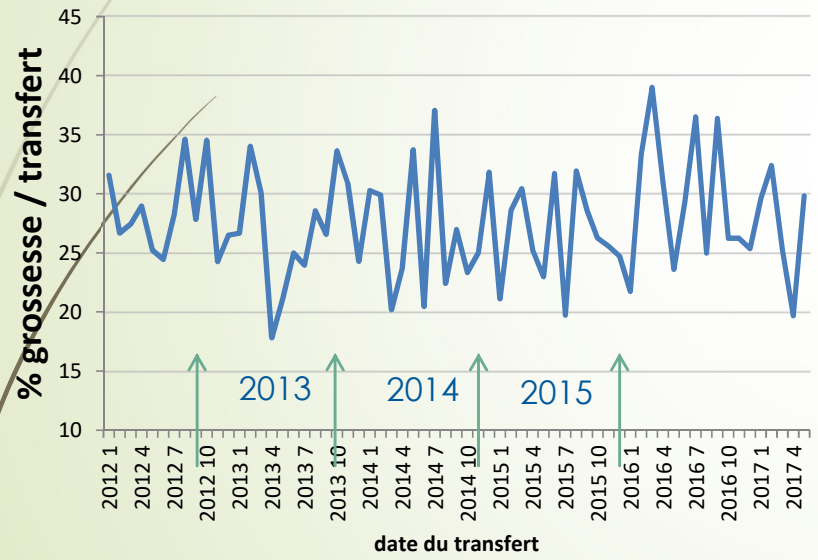
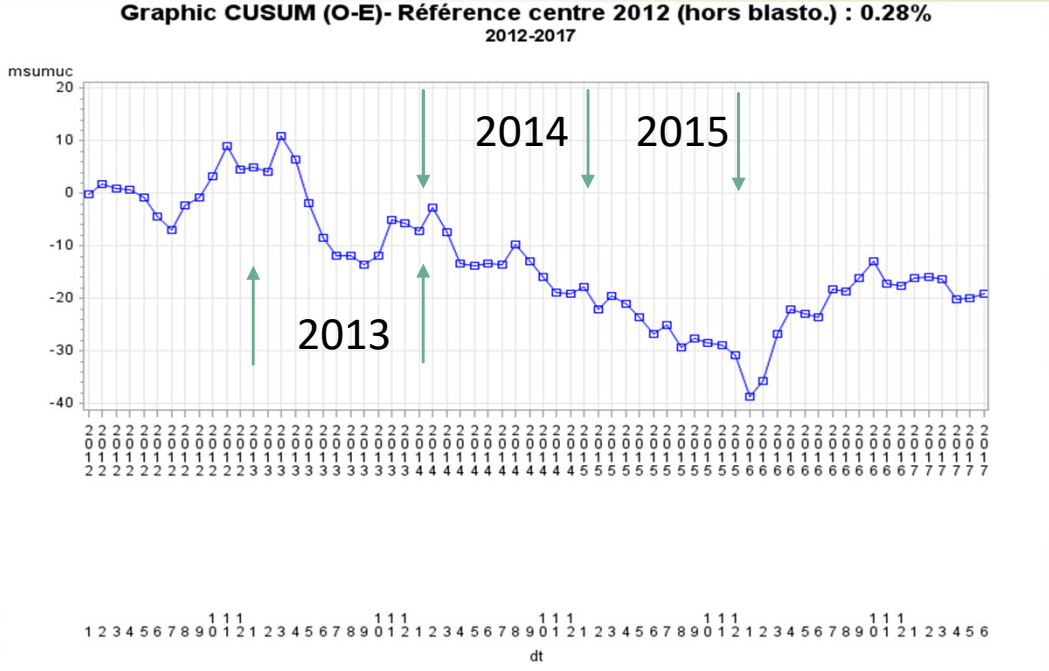
Monthly follow up of PR/Transfer



Tabular

CUSUM 2012-2017



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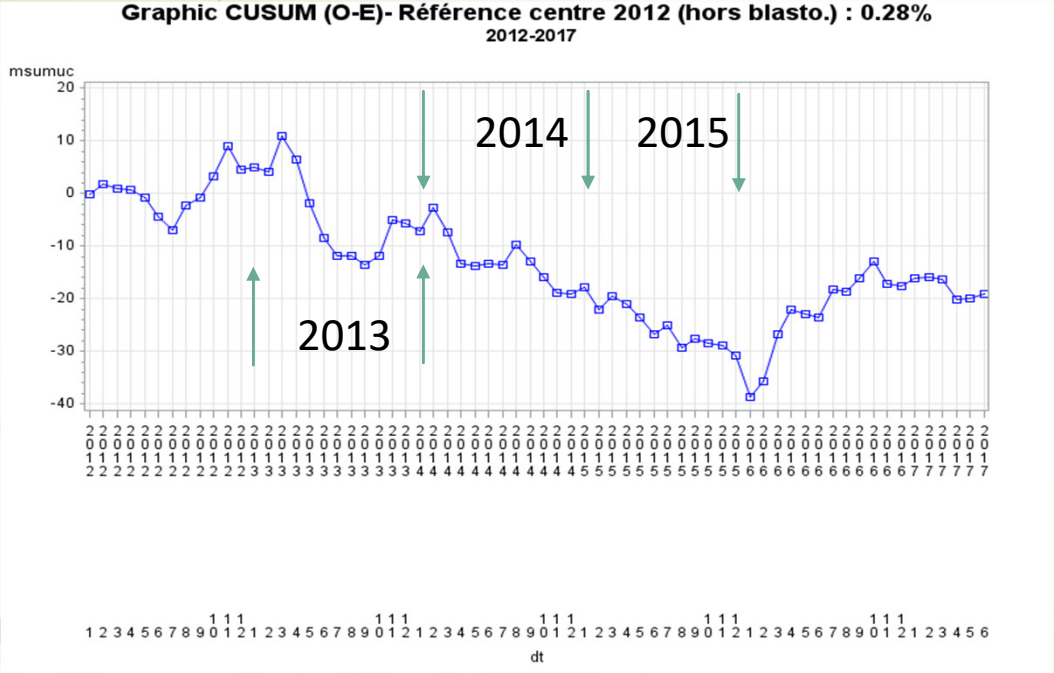
Construction of a test CUSUM

Test CUSUM for 2014-2015

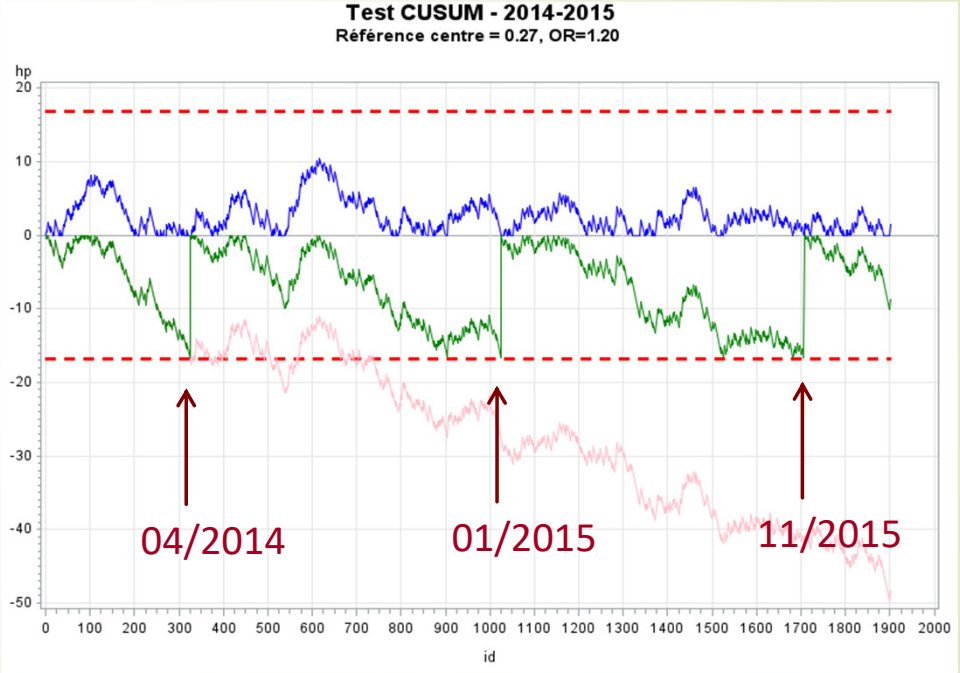
- Reference value « centre 2013 » : 27%
- Difference to detect : +/- 20%
- Sensibility : 1 false alert / 5 yrs

Tabular CUSUM 2012-2017



Test CUSUM 2014-2015

Reference 2013 = 27%



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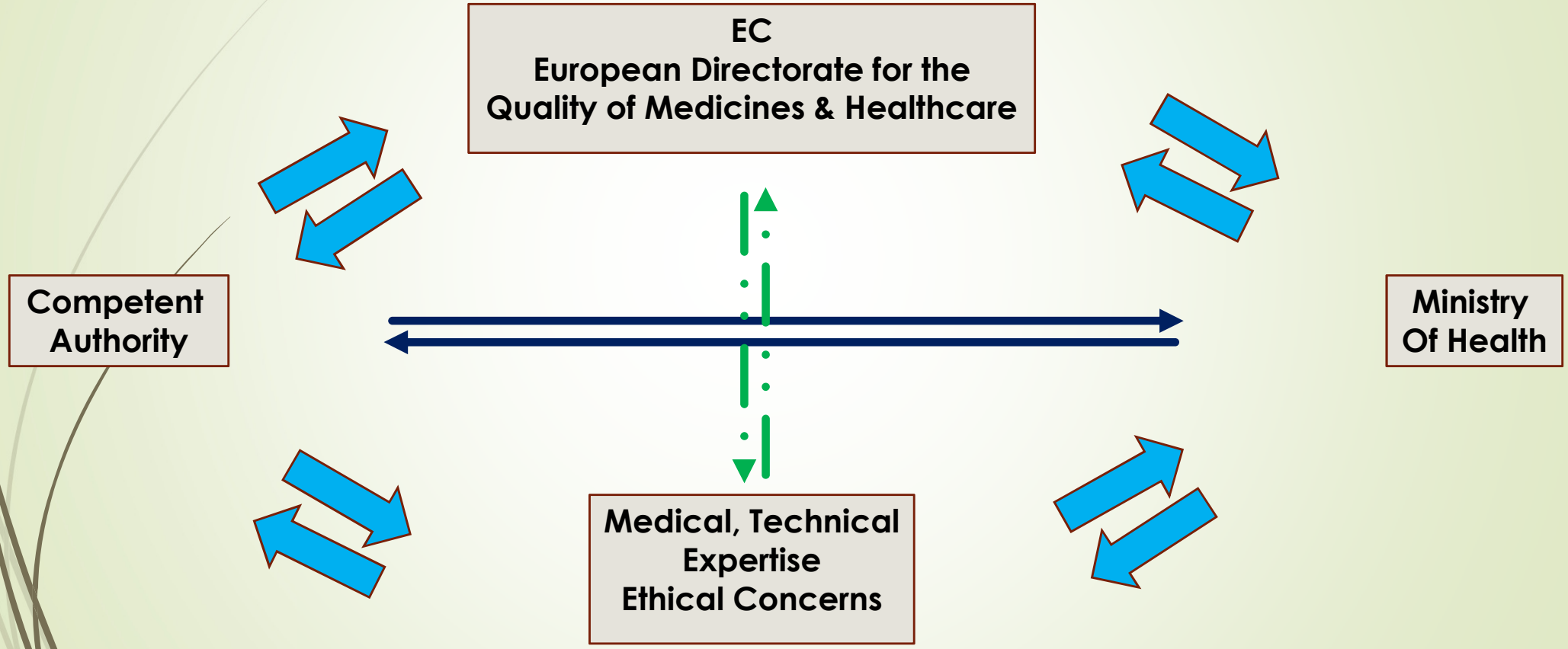

Thanks for your attention