Workshop « Scientific Integrity »
Lyon Neuroscience Research Center
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Human, Scientific and Financial Cost of Bad Professional Practice in Research and how to avoid it

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Instituts thématiques

Inserm

Institut national de la santé et de la recherche médicale

Bad professionnal practice is bad news for everyone

ÉDITORIAL

Ouvertures

Essais cliniques truqués : encore !

En 2013, en raison de fraudes sur les données cliniques, plusieurs publications d'essais portant sur le *valsartan* (Tareg® (de Novartis) ou autre) ont été rétractées par les revues concernées (a)(1,2).

Résultats flatteurs... Les résultats publiés en 2009 d'un essai comparatif randomisé semblaient montrer une efficacité importante du *valsartan* en prévention de l'angor et des accidents vasculaires cérébraux (AVC), alors que les résultats antérieurs ne montraient qu'une efficacité de faible ampleur (3,4).

Début 2013, cet article (et d'autres du même auteur japonais) a été rétracté par la revue *European Heart Journal* de la Société européenne de cardiologie, en raison de « *problèmes cruciaux* » (1).

...mais trafiqués. L'université japonaise, dont l'auteur mis en cause a démissionné, a révélé après enquête que des données brutes avaient été falsifiées pour augmenter les bénéfices en prévention de l'angor et des AVC (3). L'enquête a révélé aussi qu'une des personnes impliquées dans l'essai travaillait pour Novartis, ce que ne précisait pas l'article lors de sa publication (3).

Les enquêteurs ont refait les analyses statistiques en excluant les données des patients identifiées comme frauduleuses : les résultats corrigés ne montraient plus d'effet préventif vis-à-vis de l'angor et des AVC (3).

Problème systémique. Suite à cette première affaire, le *Lancet* a rétracté un article portant sur un autre essai réalisé au Japon sur le *valsartan*, encore avec l'implication non révélée d'une personne travaillant pour la firme Novartis (2).

Ces affaires montrent de nombreux défauts du système actuel de recherche clinique, notamment : conflits d'intérêts majeurs et dissimulés ; auteurs universitaires n'ayant pas accès aux données brutes ; publications scientifiques insuffisamment contrôlées ; rétractations d'articles peu visibles et peu explicites ; découverte de fraudes avec retard ; etc.

Une recherche clinique financée presque exclusivement par les firmes expose à d'importantes distorsions avec les faits, étant donnés les intérêts en jeu.

En pratique. L'analyse par *Prescrire* de l'évaluation du *valsartan* a été réalisée avant ces publications et reste valable. Ces afaires rappellent que les résultats d'essais cliniques ne sont pas une vérité intangible. Ils sont toujours susceptibles d'être remis en cause.

©Prescrire

a- La rétractation de ces articles est signalée dans les bases de données bibliographiques et sur le site des revues concernées.

Extraits de la veille documentaire Prescrire.

1- Barthélémy P "Scandale autour d'un médicament vedette contre l'hypertension" 21 juillet 2013. Site http://passeurdesciences.blog.lemonde.fr consulté le 27 août 2013 : 2 pages.

2- Lancet "Retraction : Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study) : a randomised, open-label, blinded endpoint morbidity-mortality study" *Lancet* 2007 ; **382** : 843.

3- Komiyama R et coll. "University admits clinical study of hypertension drug rigged" 12 juillet 2013. Site http://ajw.asahi.com consulté le 27 août 2013 : 2 pages.

4- Sawada T et coll. "Retracted : Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high cardiovascular risks: Kyoto Heart Study" *European Heart Journal* 2009 ; **30** : 2461-2469.

Whistleblower sues Duke, claims doctored data helped win $200 million in grants

By Alison McCook, Retraction Watch Sep. 1, 2016 , On a Friday in March 2013, a researcher working in the lab of a prominent pulmonary scientist at Duke University in Durham, North Carolina, was arrested on charges of embezzlement. The researcher, biologist Erin Potts-Kant, later pled guilty to siphoning more than $25,000 from the Duke University Health System, buying merchandise from Amazon, Walmart, and Target—even faking receipts to legitimize her purchases. A state judge ultimately levied a fine, and sentenced her to probation and community service.

A few examples of cost

- Dong-Pyou Han (2013, University of Iowa)
  - Fraudulently obtained 19M USD for research on a possible HIV Vaccine
  - 57 month prison and 7,2million USD sentence
  - Dismissed from University appointment
- Eric T Poelman (2006, University of Vermont)
  - Obtained 2.9M USD in grants and salary for obesity research
  - Retraction of 10 articles for fraud
  - One year prison sentence

Prevalence of Scientific Misconduct (SM) and Questionable Research Practice (QRP)

- Martinson et al, 2005, Nature 435
- Fanelli, 2009, Plos one 4
- John et al, 2012, Psychological Sciences
- ORI,2012, Annual report (Science Europe, 2015 Briefing Paper)
- Ombudsman für die Wissenschaft, 2013, (Science Europe, 2015 Briefing Paper)
- National Science Foundation, 2014, (Science Europe, 2015 Briefing Paper)

- **FFP : 2%, 10%, 20%**
- **QRP : 10%, « majority »**
- **>56%, >73% witnessed misconduct**

What is the **impact** of bad Professional Practice?(1)

- Trust in science
- Obscurantism
- Refusal to comply (vaccination)
- Danger for patients (lack of report of adverse events in clinical studies by investigators and pharmaceutical industry)

What is the **impact** of bad Professional Practice?(2)

- Late retraction* of clinical studies
  - Andrew Wakefield, Lancet : link between vaccination against measles-mumps-rubella and autism (retracted 2010, for fraud)
  - Subsequent enrolment of patients in secondary studies (2011 study : 28 000 subjects enrolled in primary studies and 400 000 in secondary studies and retraction tail * 31% of retracted papers are not notified (4Th conf on SI), (average time before retraction : 3 years)

What is the **impact** of bad Professional Practice? (3)

- Damage career of co-workers and students (Diederick Stapel, Joachim Boldt etc.)
- Damage reputation of lab and institution (Exclusion from EU funding (5 or 10 years), retraction of patents in the Hendrick Schön/ BellLab case)

What is the **impact** of bad Professional Practice? (4)

- Damage to career and life of whistle-blowers
- Damage to the scientific area (citation penalty and decrease of available funding (Science Europe, 2015 Briefing Paper))
- Waste of public money: 500 000 USD/article

What research needs : TRUST

- Funding bodies
- Co-workers, collaborators
- Scientific community (reputation)
- Society

System trust : grants and contracts

Pérenniser mon unité et lever des fonds supplémentaires

Pierre GRESSENS,
Directeur UMR 1141,
Hôpital R. Debré, Paris

« Why do our industrial partners ask for an ISO 9001 certification? »

How do you develop System trust?

- Highest standards
- Professionalism
- Honesty
- Rigour
- Ethically robust
- Accuracy
- Truth
- Reliability
- Reproducibility, …

« Norms of Science »

- Merton (1942) Norms of Science
- Singapore Statement on Research Integrity (2011)
- Montreal Statement (2013)
- ESF/ALLEA European Code of Conduct for Research Integrity (2011)

- NFX 50-553 « Management des Activités de Recherche », Afnor 2015

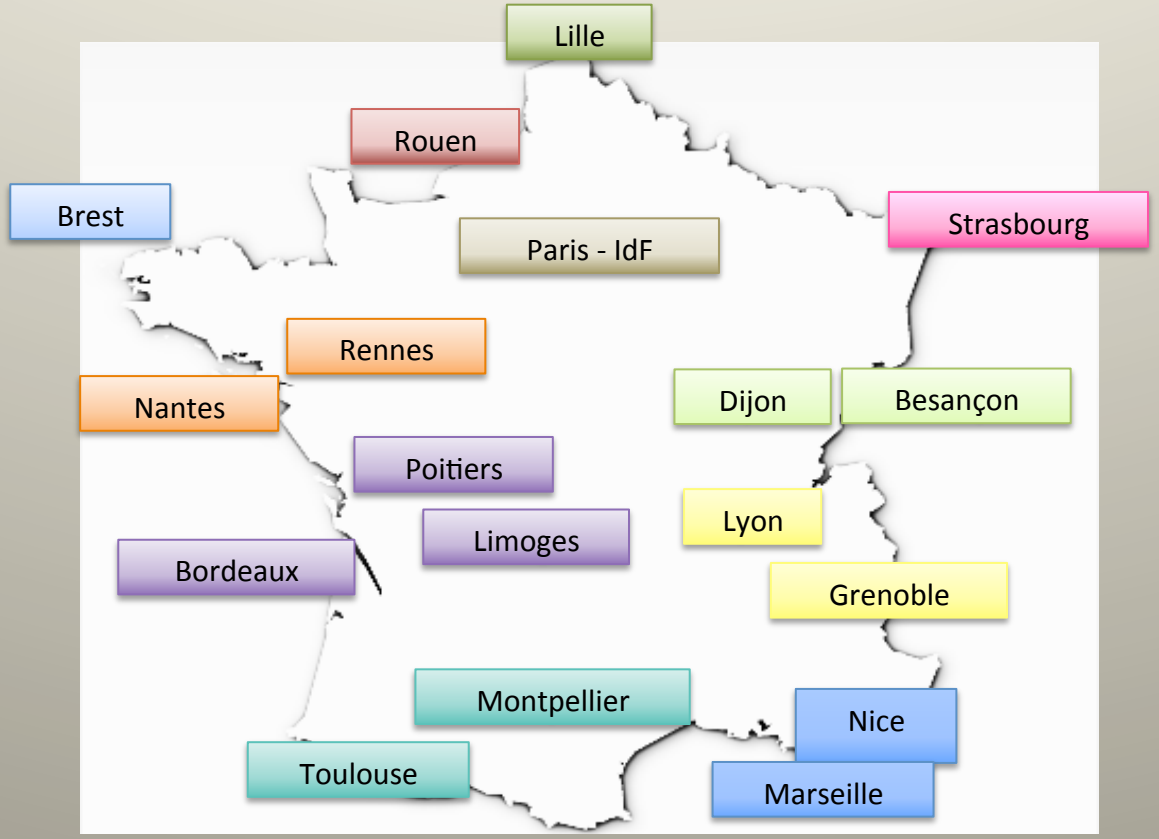
Our approach at Inserm

Management Ethique et Efficace de la Recherche (MEER)

Fair and Efficient Management of Research (Ferm)

Use Best Research Standards as guidelines and Management (project, quality, ….) tools to implement SI.

Réseau Inserm Qualité (Riq)
Inserm Quality Network



Institutionnal Quality Policy

Instituts thématiques

Inserm

Institut national de la santé et de la recherche médicale

Paris, le 1ier décembre 2014

L'Inserm recommande à ses structures de mettre en place une Démarche Qualité

En tant qu'acteur majeur de la recherche dans le domaine des sciences biomédicales, l'Inserm doit mener une recherche ambitieuse et de grande qualité. Nos recherches sont conduites avec engagement et perspicacité afin de développer notre maîtrise de sujets des plus fondamentaux aux plus appliqués. Aussi, tous les acteurs sont concernés par la pertinence, la fiabilité et la qualité du travail réalisé.

L'Inserm défend ces valeurs et répond aux enjeux sociétaux par une contribution constante de ses scientifiques à l'innovation et par son engagement en faveur de la compréhension et l'amélioration de la santé humaine.

Afin d'assurer la qualité des recherches menées, d'optimiser l'organisation des travaux et de favoriser un travail collectif équitable et efficace, l'Inserm incite ses formations de recherche et ses services à s'engager dans une Démarche Qualité.

La Démarche Qualité selon ISO 9001 est un outil de management généraliste et reconnu sur le plan international, destiné à rendre les activités plus transparentes, plus efficaces et mieux maîtrisées. Elle doit contribuer à répondre aux exigences internationales accrues, à l'évolution rapide de la recherche, à sa robustesse, à sa compétitivité et au respect de ses valeurs ainsi que à des pratiques professionnelles irréprochables. Elle a pour objectif d'améliorer la fiabilité des résultats et la traçabilité des travaux, indispensables à la publication dans des revues de haut niveau. Elle est un support à la défense de la propriété intellectuelle et contribue à une conduite responsable des projets, des équipes et des collaborations.

De multiples aides et outils sont déjà en place pour faciliter la mise en place d'un management qualité et une certification selon ISO 9001. L'Inserm dispose d'un réseau professionnel, le Réseau Inserm Qualité (RIQ), qui est en constante croissance et qui est responsable de la mise en place, du suivi et des audits qualité dans ses structures. L'Institut a renforcé son engagement et piloté la création d'une norme de recommandation pour le « Management des activités de recherche » (NFX 50 553). L'Institut incite aujourd'hui l'ensemble de ses structures et de ses personnels à s'engager dans une Démarche Qualité.

Prof. Yves Lévy
Président Directeur Général

Thierry Damerval
Directeur Général Délégué

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Different bad Professional Practices (1)

- Sloppy science
- Cherry picking of data
- Poor management (low quality mentoring, inadequate leadership, low quality of life)
- Claiming undeserved authorship/denying authorship to contributors
- Financial misconduct and abuse of a dominant position
- Fabrication, falsification, plagiat

Institutional actions against bad Professional Practice (1)

- Pierre Corvol's paper for Thierry Mandon
- ORI and Office Français de l'Intégrité Scientifique (OFIS)
- Workshops
- Délégation à l'Intégrité scientifique, Inserm
  - Ghislaine Filiatreau
  - Since 1999
  - Inserm personnel or Inserm structures
  - Recieve complaints, inquiry, mediation, report

Institutional actions against bad Professional Practice (2)

- In the institution
  - Inform, explain, teach
    - Requirement in doctoral teaching (Arrêté du 25/5/2016, article 3 NOR:MENS1611139A)
  - Organize, survey and improve
    - Ombudsman, mediator, whistle-blower

Institutional actions against bad Professional Practice (3)

- 4th conference on Research Integrity (Rio, 2015)
- European Network of Research Integrity Offices (ENRIO) (Science Europe, 2015 Briefing Paper)
  - No common approach
  - Epigenium : on-line tutorials
  - No standardised training for research integrity trainers
  - Some national coordination in Canada, Germany and Austria
- Your initiatives

Actions at the level of the Institute/ laboratory (1)

- Fair and efficient Management-Policy Declaration
  - State your commitment
  - Communicate your commitment
- Process (ISO 9001) « Fair and efficient Management»
    - Fix your aim, objective
    - Conduct actions and measure their efficiency
    - Check for defaults
    - Improve system stepwise

Singapore Statement on Research Integrity

Preamble. The value and benefits of research are vitally dependent on the integrity of research. While there can be and are national and disciplinary differences in the way research is organized and conducted, there are also principles and professional responsibilities that are fundamental to the integrity of research wherever it is undertaken.

PRINCIPLES

Honesty in all aspects of research

Accountability in the conduct of research

Professional courtesy and fairness in working with others

Good stewardship of research on behalf of others

RESPONSIBILITIES

1. Integrity: Researchers should take responsibility for the trustworthiness of their research.

2. Adherence to Regulations: Researchers should be aware of and adhere to regulations and policies related to research.

3. Research Methods: Researchers should employ appropriate research methods, base conclusions on critical analysis of the evidence and report findings and interpretations fully and objectively.

4. Research Records: Researchers should keep clear, accurate records of all research in ways that will allow verification and replication of their work by others.

5. Research Findings: Researchers should share data and findings openly and promptly, as soon as they have had an opportunity to establish priority and ownership claims.

6. Authorship: Researchers should take responsibility for their contributions to all publications, funding applications, reports and other representations of their research. Lists of authors should include all those and only those who meet applicable authorship criteria.

7. Publication Acknowledgement: Researchers should acknowledge in publications the names and roles of those who made significant contributions to the research, including writers, funders, sponsors, and others, but do not meet authorship criteria.

8. Peer Review: Researchers should provide fair, prompt and rigorous evaluations and respect confidentiality when reviewing others' work.

9. Conflict of Interest: Researchers should disclose financial and other conflicts of interest that could compromise the trustworthiness of their work in research proposals, publications and public communications as well as in all review activities.

10. Public Communication: Researchers should limit professional comments to their recognized expertise when engaged in public discussions about the application and importance of research findings and clearly distinguish professional comments from opinions based on personal views.

11. Reporting Irresponsible Research Practices: Researchers should report to the appropriate authorities any suspected research misconduct, including fabrication, falsification or plagiarism, and other irresponsible research practices that undermine the trustworthiness of research, such as carelessness, improperly listing authors, failing to report conflicting data, or the use of misleading analytical methods.

12. Responding to Irresponsible Research Practices: Research institutions, as well as journals, professional organizations and agencies that have commitments to research, should have procedures for responding to allegations of misconduct and other irresponsible research practices and for protecting those who report such behavior in good faith. When misconduct or other irresponsible research practice is confirmed, appropriate actions should be taken promptly, including correcting the research record.

13. Research Environments: Research institutions should create and sustain environments that encourage integrity through education, clear policies, and reasonable standards for advancement, while fostering work environments that support research integrity.

14. Societal Considerations: Researchers and research institutions should recognize that they have an ethical obligation to weigh societal benefits against risks inherent in their work.

The Singapore Statement on Research Integrity was developed as part of the 2nd World Conference on Research Integrity, 21-24 July 2010, in Singapore, as a global guide to the responsible conduct of research. It is not a regulatory document and does not represent the official policies of the countries and organizations that funded and/or participated in the Conference. For official policies, guidance, and regulations relating to research integrity, appropriate national bodies and organizations should be consulted. Available at: ***www.singaporestatement.org***

Actions at the level of the Institute/ laboratory (2)

Possible objectives/actions

- **Singapore Statement : 1. Integrity:** Researchers should take responsibility for the **trustworthiness** of their research.

- **Singapore Statement : 3. Research Methods:** Researchers should employ appropriate research **methods**, base conclusions on **critical analysis** of the evidence and report findings and interpretations fully and objectively
  - ***Metrology/Methodology/Statistics***

- **Singapore Statement : 4.** Research Records: Researchers should keep clear, accurate records of all research in ways that will allow **verification** and **replication** of their work by others.
  - ***Documentation, lab log book, publi-box***

Added value by Ferm (1)

- Metrology:
  - Identify critical equipments
  - Check at appropriate time intervals
  - « Qualify » equipment
  - Inform co-workers

Added value by Ferm (2)

- Documentation : Transparency and traceability

  – Collect data and related information

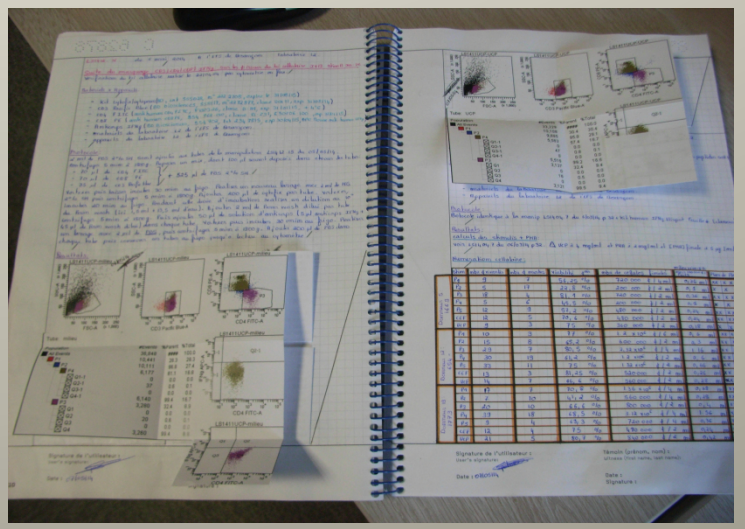
  – Organize information suitable for proof (publi-box)

  – Protect information from loss and unavailability

6. Singapore Statement : Authorship: Researchers should take responsibility for their **contributions** to all publications, funding applications, reports and other representations of their research. Lists of authors should include all those and only those who meet applicable **authorship criteria**

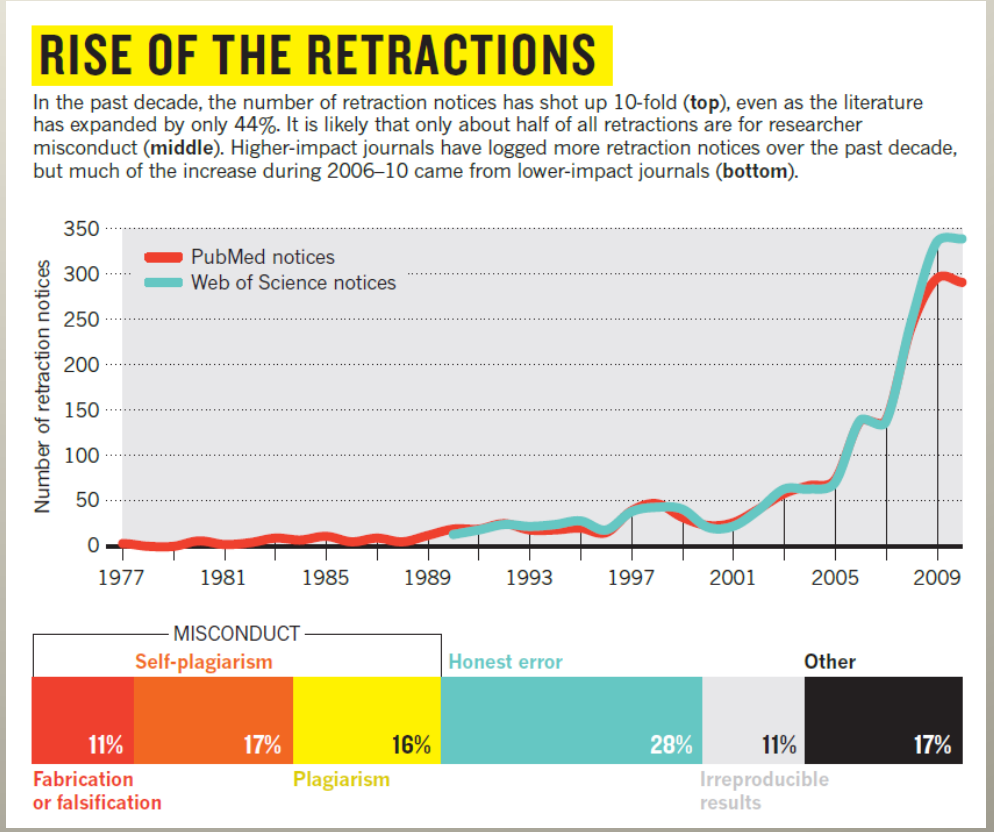
7. Singapore Statement : Publication Acknowledgement: Researchers should **acknowledge** in publications the names and roles of those who made significant contributions to the research, including writers, funders, sponsors, and others, but do not meet authorship criteria.

- **Laboratory log book**
  - Quality of proof
  - Keep in the lab
  - Make copy for user
  - Explain ownership of data, of thesis report, …
  - Use as proof when needed
    - Questionning by scientists
    - Request of journal
    - Patent issues



Avoid retraction

- Loss of trust
- Reputation
- Financial loss
- Unethical behavior



Retractions of articles and their causes (van Noorden, Nature 478, 2011)

Inform, explain : Flow chart (1)

2. Adherence to Regulations: Researchers should be aware of and adhere to **regulations** and policies related to research.

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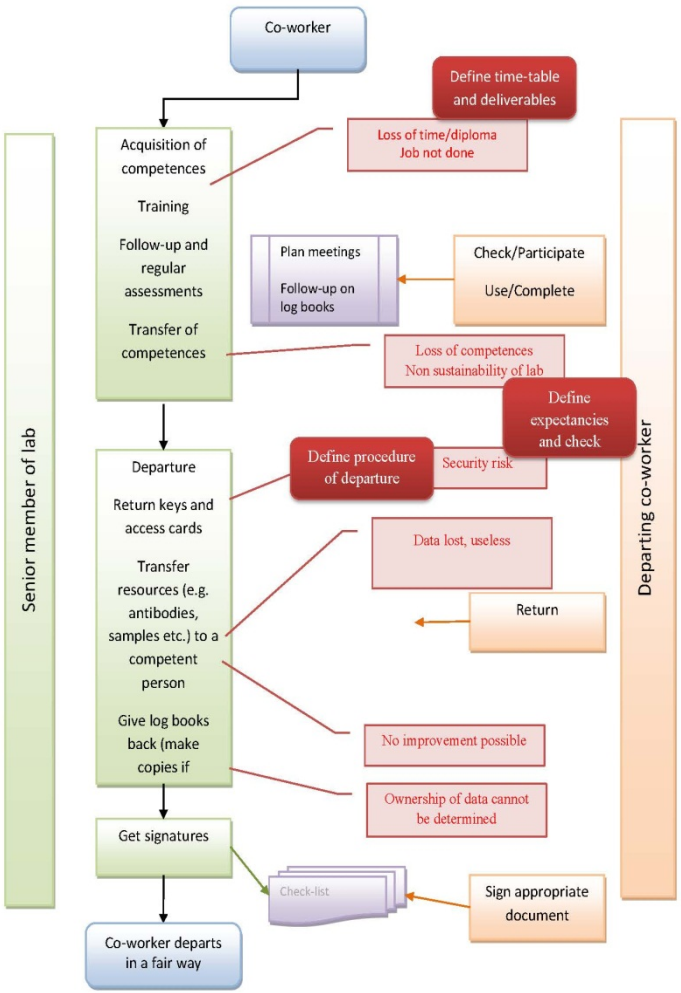
Inform, explain : Flow chart (2)

Figure 7 Departure of a co-worker



Why do people behave badly?

- **Research funding**
  - Success rates for public funding < 20%, EU Horizon 2020 : 14%
- **Career development**
  - Publish or perish
    - Fraudulent authors target high impact-factor journals
    - Check quality of peer review
    - Replication studies
    - Negative results
    - Predatory journals
  - Financial incentives (portions of salary)
  - Evaluation criteria for scientists
- **Strive for fame**
  - Innovative, important research, « glamour » of topic
  - 'Titelsucht'

Quality management helps create a culture of Integrity

- Supportive environment (Fanelli, 2009) : promote research integrity policies, improve mentoring, encourage transparency)
- Quality management (don't pin down the wrong-doer, but improve collectively and step by step)
- Process "Best Professional Practice"

Is it possible to influence the behavior of scientists?

- Seentashore et al (2007) : organizational climate
- Mumford et al (2007) : environmental influences on ethical decision making
- Martinson et al (2010) : organizational justice and positive behaviors
- European commission(2015) : 8 criteria governance, public engagement, gender equality, science education, open access/open science, ethics, sustainability, social justice

Is it possible to change the evaluation of scientists?

Is it possible to change the funding structure of research?

Some readings from the Riq

- **Boulanger V, Brémard S, Descombes S, Mura AM, Giesen E (2011) Le management qualité en animalerie. Sci Tech Anim Lab 37/4, 15-90**
- **Alvarez M, Arnaud JD, Chevalier C, Lottin Y, Philippe A, Giesen E 2014, Management qualité en recherche. Gestion électronique de la documentation dans un laboratoire ou service, Stal 40/3, 31-45**
- **Martin L, Moreau E, Giesen E 2014, Conservation et stockage de données et de documents scientifiques afin de faciliter la sauvegarde et l'accessibilité aux laboratoires et dans les services de zootechnie. Stal 40/2, 33-54**
- **Giesen E et al Ethical and efficient research management: a new challenge for an old problem. Int.J. Qual. Eng. 2015, 6, 460-471**
- **Giesen E Quality management for robust and reliable research, Int. J. Metrol. Qual. Eng. 2016, 6, 407-417**
- **Mura AM, Lottin Y., Arnaud JD, Gall V, et Giesen E. (2016) L'animalerie prise en tenaille. Stal, 42/1, 27-36**
- **Arnaud JD, Chauffeton, V., Gall V., Mura AM., Giesen E. (2016) Manager un service de zootechnie pour favoriser la qualité de vie au travail, Stal 42/2, 1-9**
- **Lottin Y et al, (soumis à Stal2017) Manquons-nous de qualité de vie en zootechnie?**

Do you have any questions ?