agence d'évaluation de la recherche
et de l'enseignement supérieur

Department for the evaluation of research units

AERES report on unit:

Epidemiology and biostatistics Sorbonne Paris Cité

Under the supervision of the following institutions and research bodies:

Université Paris Descartes

Institut national de la santé et de la recherche médicale

January 2013

agence d'évaluation de la recherche
et de l'enseignement supérieur

Research Units Department

President of AERES

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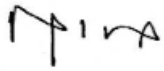
Department Head



Pierre Glaudes

The president of AERES "signs[...], the evaluation reports, [...]countersigned for each evaluation department by the relevant head of department (Article 9, paragraph 3, of french decree n°2006-1334 dated 3 november 2006, revised).

Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).

This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.

NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

Criterion 1 - C1 : Scientific outputs and quality ;
Criterion 2 - C2 : Academic reputation and appeal ;
Criterion 3 - C3 : Interactions with the social, economic and cultural environment ;
Criterion 4 - C4 : Organisation and life of the institution (or of the team) ;
Criterion 5 - C5 : Involvement in training through research ;
Criterion 6 - C6 : Strategy and five-year plan.

With respect to this score, the research unit concerned by this report and its in-house teams received the following grades:

- Grading table of the unit: Epidemiology and biostatistics Sorbonne Paris Cité

C1	C2	C3	C4	C5	C6
A+	A+	A+	A	A+	A

- Grading table of the team: Perinatal Epidemiology, Obstetric and Pediatric

C1	C2	C3	C4	C5	C6
A+	A+	A+	A+	A+	A+

- Grading table of the team: Biostatistics and Clinical Epidemiology

C1	C2	C3	C4	C5	C6
A+	A	A	A	A+	A

- Grading table of the team: Nutritional Epidemiology

C1	C2	C3	C4	C5	C6
A+	A	A+	A+	A+	A+

- Grading table of the team: Clinical Epidemiology applied to osteo-articular diseases

C1	C2	C3	C4	C5	C6
A+	A	A	NN	B	B

- Grading table of the team: Method of therapeutic evaluation Chronic diseases

C1	C2	C3	C4	C5	C6
A+	A+	A+	A	A+	A+

Evaluation report

Unit name:	Epidemiology and biostatistics Sorbonne Paris Cité
Unit acronym:	
Label requested:	UMR-S
Present no.:	Ms Sylvie CHEVRET (UMRS 717), Mr François GOFFINET (UMRS 953), Mr Serge HERCBERG (UMR 557 INSERM-U1125, Inra, CNAM), Mr Philippe RAVAUD (UMRS 738)
Name of Director (2012-2013):	Ms Sylvie CHEVRET, Mr François GOFFINET, Mr Serge HERCBERG, Mr Philippe RAVAUD
Name of Project Leader (2014-2018):	Mr Philippe RAVAUD

Expert committee members

Chair:	Mr Christophe TZOURIO, Université Bordeaux 2
Experts:	Ms Claire BONITHON-KOPP, Université de Bourgogne
	Ms Marcela GONZALES, Universidad Politécnica de Madrid, Spain
	Ms Hélène JACQMIN-GADDA, Université Bordeaux 2 (representative of CSS INSERM)
	Mr Peter JÜNI, University of Bern, Switzerland
	Mr Christoph RUDIN, University Children's Hospital of Basel, Switzerland
	Ms Anne-Marie SCHOTT-PETHELAZ, Hospices Civils de Lyon (representative of CNU)
	Ms Camilla STOLTENBERG, Norwegian Institute of Public Health, Norway
	Ms Claire THORNE, London Institute of Child Health, UK

Scientific delegate representing the AERES:

Ms Valériane LEROY

Representative(s) of the unit's supervising institutions and bodies:

Ms Christine CLERICI, Université Paris Diderot

Mr Charles DESFRANCOIS, Université Paris Bobigny

Mr Arnaud DUCRUIX, Université Paris Descartes

Mr Michel EDDI, INRA

Ms Clotilde FERROUD, CNAM

Ms Isabelle HENRY, INSERM

1 • Introduction

History and geographical location of the unit

The PRES (« Pôle de Recherche et d'Enseignement Supérieur ») Sorbonne Paris Cité includes 8 partners in Paris: four Universities (Paris Descartes, Paris Diderot, University Paris 13 Nord and Sorbonne nouvelle) and four "elite institutes" (Sciences-Po, Institut de Physique du Globe, Institut National des langues et civilisations orientales, Ecole de Hautes Etudes en Santé Publique).

Within the PRES Sorbonne Paris Cité, the Epidemiology and Biostatistics Sorbonne Paris Cité Research Centre is dedicated to epidemiology, with a strong emphasis on clinical epidemiology but also descriptive and interventional epidemiology, biostatistics, and comparative effectiveness research.

It will combine five research teams as follows:

- Team 1: Perinatal, Obstetrical and Paediatric Epidemiology (head: Mr Pierre-Yves ANCEL), currently located in the Maternity Port-Royal and Cochin Hospital;
- Team 2: Biostatistics and Clinical Epidemiology (head: Ms Sylvie CHEVRET), currently located in Saint Louis Hospital;
- Team 3: Nutritional Epidemiology (head: Mr Serge HERCBERG), currently located in Avicenne Hospital;
- Team 4: Clinical Epidemiology of Diseases of the Musculoskeletal System and Connective Tissue (head: Mr Serge POIRAUDEAU), a new emerging team, currently located in Cochin Hospital;
- Team 5: Therapeutic Evaluation Methods for Chronic Diseases (head: Mr Philippe RAVAUD), currently located in Hotel Dieu.

Four of these teams derive from four different INSERM units that existed in the previous four-year plan:

- UMR S953 INSERM, entitled Perinatal, Obstetrical and Paediatric Epidemiology directed by Mr François GOFFINET, Pierre-Marie Curie University/ Paris Descartes University /Paris Sud University;
- UMR 717 INSERM, on Biostatistics and Clinical Epidemiology directed by Ms Sylvie CHEVRET, Paris Diderot University;
- U557 INSERM /U1125 Inra/CNAM/ University Paris 13 Nord on Nutritional Epidemiology directed by Mr Serge HERCBERG;
- Team 2 of the UMR 738 INSERM, "Models and Methods of Therapeutic Evaluation of Chronic Diseases" in Diderot University directed by Mr Philippe RAVAUD (France Mentré was in charge of the UMR 738).

Two of these teams are much larger than the others: Team 1 (63 permanent staff) and Team 3 (66 permanent staff) compared to the other ones (Team 2: 19, Team 4: 11, and Team 5: 20). Team 1 and 3 are also strongly involved in data acquisition through large cohorts or registries which is not the case for the other teams except for team 4 but on a much smaller scale. At present, these teams are in different locations although most are in the inner Paris. Team 3 is located in the north-east suburbs (Avicenne).

Management team

Mr Philippe RAVAUD will be the director.

AERES nomenclature

SVE1_LS4 Physiology, physiopathology, medical systems biology

SVE1_LS6 Immunology, microbiology, virology, parasitology

SVE1_LS7 Epidemiology, public health, clinical research, biomedical technologies

SHS1_1 Economics

SHS2_4 Sociology, Demography

Unit workforce

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	58	60	60
N2: Permanent researchers from Institutions and similar positions	21	19	19
N3: Other permanent staff (without research duties)	24	25	10
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	0	0	0
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	8	11	11
N6: Other contractual staff (without research duties)	67	67	26
TOTAL N1 to N6	178	182	126

Percentage of producers	***100 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	43	
Theses defended	41	
Postdoctoral students having spent at least 12 months in the unit*	12	
Number of Research Supervisor Qualifications (HDR) taken	16	
Qualified research supervisors (with an HDR) or similar positions	45	56

2 • Assessment of the unit

Strengths and opportunities

- Project based on excellent teams with a very high level of scientific production and a proven ability to raise funds.
- The desire to work together and to build the centre is clearly expressed.
- Consistency of the project in terms of policy and institutional strategies.
- Unique position in France in clinical epidemiology.
- Several potential future leaders among young researchers.

Weaknesses and threats

- Projects of collaborations, sharing resources and infrastructure are still limited.
- Location on multiple sites is an issue which seems to have no short-term solutions.
- The scientific strategy of the centre and particularly the interactions between teams is not matured enough. Only few common cross-cutting projects have been envisaged so far.
- Most teams have experienced difficulties attracting foreign researchers, particularly post-doc students.

Recommendations

- To carry on in depth discussions in order to have an appropriate strategy to set up and develop the centre for the next 5 years. This could include to encourage bottom-up cross-cutting projects between teams which are essential for building the centre. Common projects should be encouraged as a first and foremost goal of the centre and should be supported by dedicated means coming from or raised by the various teams.
- To reinforce and to innovate scientific animation in order to overcome the limitation of multiple sites; partial grouping of forces and setting up of common premises at the Hotel-Dieu could also help in that matter.
- To build a common strategy for developing and sharing research infrastructures such as biobanks and large databases.
- To improve attractiveness toward foreign researchers and post-doc students by joining means and forces.
- To implement a policy to encourage the emergence of: 1) new teams and in particular teams of clinicians in various specialties, probably after an incubation phase within a larger team of epidemiologists 2) future leaders within the teams.

3 • Detailed assessments

Several points were discussed at length during the visit - with all of the executive committee and head-to-head with each of the leaders - either because they are essential in the creation of a research centre or because they are specific to the centre assessed. It is important to note that the hearings have clarified a number of important elements that were not presented explicitly or in detail in the written document. The questions asked by the committee members have also clarified some strategic elements. We have summarized the discussions on these points below.

Assessment of scientific quality and outputs

Quality of the teams

As detailed in the individual reports, the committee evaluated the teams as very good or excellent for most of the criteria. One emerging team (Team 4) was not at the same high level although it is very efficient to raise funds for its projects and has a very good level of publication. This team would perhaps benefit of a longer maturation - particularly in terms of elaborating a sound scientific project - within another more experienced team. The committee sees as of major importance the collaboration with teams of clinicians within a centre largely dedicated to clinical epidemiology. If, in the future, the centre was willing to individualise such teams of clinicians, a stronger epidemiological coaching might be necessary before the evaluation.

All the teams have proven their ability to raise funds. The total amount of funds during the past 5 years was about 40 M€, mainly from the public sector, and the largest part from Inca or PHRC (14M€). European grants were less than 10% of the total amount (3.7M€) and to increase this percentage was presented as a future goal of the centre.

Assessment of the unit's academic reputation and appeal

All the teams have an excellent academic reputation and visibility. Like for most of French research labs, the teams have experienced difficulties attracting foreign researchers (particularly post-doc students). If the centre was created, they could join their forces in order to improve this aspect.

Assessment of the unit's interaction with the social, economic and cultural environment

All the team’s research findings have an important impact on public health policies and practices at both international and national levels.

Assessment of the unit's organisation and life

Governance

The candidate director of the centre, Mr Philippe RAVAUD undeniably has both the capacity and experience to implement an adequate governance. The scheme proposed is a classical direction with appropriate bodies to operate with a sufficient degree of information and participation of various staff members. The executive committee would comprise the director, the general secretary (or deputy director), the heads of the various teams, and representatives of staff members and students. With regard to the choice of director, the committee interviewed each team leader and concluded that this choice seemed coherent and indisputable not only because of his qualities as a researcher and team leader, but also due to his comprehensive knowledge of the institutional landscape.

It should be noted that all team leaders have achieved a sufficient level of scientific maturity and experience of team management for a dialogue of equals in the steering committee. The visiting committee identified a number of younger researchers that seem qualified to assume leadership roles in the future. If the centre is to be established, it is important that governing bodies have a proactive approach to identifying, training and promoting these researchers to gradually put them in a position of leadership.

Institutional support

As PRES Sorbonne Paris Cité has not yet been created, institutions bearing the project are INSERM and University Paris Descartes but all were present and with a high level of representation (head of the department of Evaluation and programme's monitoring at INSERM, president or vice-president of university, dean of Faculty of Medicine, etc.). The overall support is unanimous and unambiguous. Institutions all said that the field of public health and clinical epidemiology were privileged areas of development for their structure in the years to come. It was also noted that the proposed centre fits naturally in the PRES project and would be an important component of it. Institutions expressed their agreement in principle to a pooling of their help in order to create a position of General Secretary which is expressed repeatedly as a need and for the renovation of premises at the Hotel-Dieu to accommodate the team 1.

Location and scientific animation

The relative dispersal of teams on different sites was a recurring issue during the evaluation visit. This question was partially anticipated by the project partners in the written document in which they emphasize the density of the transport network in Paris and suburbs, the fact that several teams were already working on several sites and were therefore getting used to it, and the possibility of using videoconferencing for a number of meetings.

The future of the Hôtel-Dieu, which is still under discussion and with an unknown schedule, was discussed at meetings with project leaders as well as at the meeting with the institutions. Allocation and refurbishment of premises on a single site, to accommodate some of the teams could be seen as a solution to the current problem of scattering. However, the importance of the local implementation of teams (including staff with hospital functions) does not make a grouping of all of them on the same site likely or feasible in the near future. If space was available at some point at the Hôtel-Dieu, the project partners are orientated more towards the establishment of common premises, such as meeting rooms or temporary offices. Although committee members had nuanced opinions on the need for physical proximity of different teams, it remains that the geographical dispersal could be seen as a weakness.

One way to try to overcome this relative scattering is to put in place a dense and attractive scientific animation. The committee felt that this issue had not yet received the appropriate attention. The proposed informal meeting between junior and senior researchers (speed dating) was seen as an interesting suggestion. Proposals for scientific meetings seem rather standard whereas a stronger dynamic would be expected including retreats or high-level conferences on cross-cutting issues.

Assessment of the unit's involvement in training through research

Staff, students, teaching and training

Meeting with the staff members showed that they were generally satisfied with their current working conditions and relationships with researchers and their supervisors. Communication about the project of centre was variable depending on the teams. There was no expression of particular concern with regard to the creation of the centre, which was seen as quite positive and could offer opportunities in terms of job creation and exchanges between the different teams. The creation of the centre could also be the opportunity to have access to the different training offered by the institutions, which is not currently the case (e.g. an engineer or technician INSERM has no access to training given by the CNAM). During the meeting with the institutions this request was received favourably.

A general problem is the large proportion of technicians and engineers that are on temporary positions in most teams, with a number of them nearing the contract limit. Solutions are been actively sought but the discontinuation of some contacts may be highly detrimental to the teams given the know-how these personnel centralize.

Meeting with the students showed that they also had satisfactory working conditions and had sufficient access to their supervisor and team resources. They all have adequate financial support and also have the opportunity to attend regularly meetings abroad. The meeting with all the researchers was also very positive, confirming their commitment on this project and making it clear that there were potential leaders among young researchers, as said above.

Most of the teams are heavily involved in teaching, probably in part because a majority of researchers are permanent professors or equivalent. They are involved (executive board members) in the two doctoral schools in public health in Paris and in several master's training in their University (Paris 5, 7, and 13). Several teams are working together on a new master's degree in English. Altogether, 80 master students are trained each year in the teams and there are about 40 PhD students. These are very good figures for a total of 45 researchers with an accreditation to supervise research (HDR).

Assessment of the five-year plan and strategy

Process of project development and overall consistency

Based on the written document, the committee members felt that the centre was designed more in a federal manner than as a unification and synergy of constituting forces. The approach seemed indeed quite cautious with a limited willingness of sharing. For example, it is written in the document and reiterated during the oral presentation that there will be no pooling of financial resources. This is understandable in the case of individual research projects but seems less relevant with regard to recurrent allocations provided by institutions. Mutual funds could notably enable communication operations and internal scientific animation. It could also help with the emergence of young teams without waiting for a funding through calls. Another example is the lack of emphasis for creating common resources and infrastructure such as shared data collections or the biobank established by team 3. It was said that there is no intention to develop cross-sectional axes on the basis that these would be, mostly, artificial creations. The committee underlines, however, that collaboration on joint projects promotes interaction between researchers and between teams and that thoughts on this subject should be further developed if the centre is created.

Several factors have emerged during the visit that modulates what might appear as a potential weakness on the project: 1) The proposed centre is a de novo creation. The first incentive was institutional and responds to a logic of top-down structuring research in Paris. This logic, although understandable, nevertheless explains the lack of in-depth reflection on joint projects to strengthen the coherence of the proposed centre. 2) The maturation period was short because the discussions between teams started less than a year ago. 3) The written project reflects poorly the willingness of the teams to work together which only became clear, and on several occasions, during the visit.

Strategy

The committee asked each team leader to summarize their main motivation for creating this centre. The answer most frequently put forward was the increased visibility that this would bring. Team leaders expect to be better recognized vis-à-vis their institutions and administrative authorities, and the scientific community at national and international levels. The possibility of obtaining permanent positions including engineers and technicians was also frequently mentioned. Pooling of resources and experience and the setting up of joint projects across teams were also cited but often last. They were exposed more as general principles than as projects that could be really done in a short to medium term if the centre was created. As was said earlier, this could be in a large part due to the relatively short time of discussion but these issues need to be discussed further in details if the centre is created.

It appeared to the committee that the overall scientific strategy and positioning of the centre at national and European level in the next five years have generally not been conceived in depth. The future director stressed that clinical epidemiology was a major characteristic of this centre which will then be unique in France. The committee approves this line of thinking as it would give a clear identity to the centre. It is expected that, if the centre is created, this strategic thinking should be developed with stronger indications of aims and milestones than in the present document.

Concerning the local strategy, it is important to note that this project covers part of the perimeter of the future PRES. The creation of this centre is therefore consistent with the PRES and strongly supported in this context (see section on institutions). However the PRES does not exist so far, which complicates certain administrative aspects for the present application.

To summarize, at this stage the institutional logic or policy may seem more prominent than scientific strategy in this project. However, because of the high quality of the individual teams which have proven their ability to elaborate a consistent scientific strategy, the committee is confident that the centre will go beyond the simple addition of present forces, i.e. the whole will be greater than the sum of its parts.

4 • Team-by-team analysis

Team 1: Perinatal Epidemiology, Obstetric and Pediatric

Name of team leader: Mr Pierre-Yves ANCEL

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	24	22	22
N2: Permanent EPST or EPIC researchers and similar positions	7	5	5
N3: Other permanent staff (without research duties)	6	6	5
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	5	5
N6: Other contractual staff (without research duties)	22	21	17
TOTAL N1 to N6	62	59	54

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	13	
Theses defended	18	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	6	
Qualified research supervisors (with an HDR) or similar positions	16	22

• Detailed assessments

Assessment of scientific quality and outputs

This team is built on a long-standing unit addressing perinatal and child health, with a broad scope of research in clinical epidemiology in these fields. The central themes of the research to date have been broadly divided into two key areas: evaluation of the organization of and clinical practices in perinatal health care, and aetiological research. The team has demonstrable expertise in a range of methodologies as applied to perinatal health including population-based cross-sectional surveys, cohort studies, registries, randomized controlled trials and systematic reviews, and plan to build on this in their proposed programme of work. The team has established a number of national multicentre cohort and population-based studies, for example, EPIPAGE and EPIPAGE-2, which address outcomes in very preterm infants; EPICARD – a cohort of children with congenital heart defects; EPIMOMS – a study of severe maternal mortality), and additionally co-ordinates and participates in several international (European) studies (EUROPERISTAT; EPICE). They have therefore produced or contributed to the production of several large and important databases and cohorts.

The team has an impressive track record with respect to publications, with the total number of annual papers in international journals increasing from around 30 to around 50 over the past five years: out of the 317 peer-reviewed publications over the last five years, 172 were led by the team 1 (54%). Around half of these papers as leaders in 2012 were published in top specialty journals (Obstetrics and Gynaecology, Pediatrics, Journal of Pediatrics, British Journal of Obstetrics and Gynaecology, Am Journal of Obstet Gynecol…). Although only few publications were in the top 5% general journals (Lancet2008, JAMA 2008, BMJ open 2011 and 2012, Lancet Oncology 2012). Given the available data and the number of researchers in this team, the committee believes that the number of high quality scientific outputs could be (and should be) even larger in the future. It should be noted that the key results of this team have had some important implications for evidence-based perinatal care and have informed clinical guidelines and policy-makers.

Assessment of the unit's academic reputation and appeal

The team has a strong national academic reputation – and appears to occupy the key niche in perinatal epidemiological research in France, with many years of activity in this field within the team. The team leads several national studies and collaborates on numerous other studies in France. It is clear that they are recognised experts in this area of research, and enabling and advisory activities with colleagues in other research units are apparent. Furthermore, the team attracts a considerable number of Masters and PhD students annually, an excellent reflection of its visibility and standing. The team has attracted an international post-doc researcher, demonstrating some international academic visibility.

Importantly, the team has some key international collaborations and partnerships, and leads or participates in a number of European projects (EUROPERISTAT; EPICE; PREVUR and PREMEN). The team is involved in governance of several of these large-scale international networks (e.g. representatives in Executive Boards of EUROCAT; EPEN; INOSS). There are also international partnerships with other research teams in Europe, Canada and the United States.

Acquisition of research funding from national and international bodies is really outstanding – there have been 65 research contracts with national and international bodies since 2007, having resulted in the impressive total sum of €18 million, which excludes salary support for tenured researchers. The current head of the team received a substantial prize in 2010 from the Bettencourt-Schueller Foundation for relocation / refurbishment of the team at Port-Royal Hospital.

Senior team members have been invited as speakers to international meetings, they act as peer reviewers for national and international journals and funding bodies, sit on editorial boards of one international and national journal each and participate in scientific committees for international and national meetings and conferences. However the committee believes that, on the basis of the scope of their research and their research income, this team could have an even greater reputation than it presently has. This could probably be achieved in a variety of ways in the future, for example, through extending their networks by making existing databases more accessible to the national and international research community for nested projects and through the new international Masters programme.

Assessment of the unit's interaction with the social, economic and cultural environment

The team's research findings have had an important impact on public health policies and practices in the past. For instance, research findings from this group demonstrated that mucolytics are not only ineffective but even risky in children aged less than 2 years; this led to approval of mucolytics for this age group being withdrawn. Another example is the identification of post-partum haemorrhage as the major maternal mortality risk factor in France, which led to an adaptation of the clinical recommendations how to prevent and how to deal with this postpartum complication. Of note, the team developed a reference list of perinatal indicators, which has not only been used within European networks, i.e. EUROPERISTAT and EUROCAT, but also served to highlight the inadequacies of routine perinatal data collection in France, with resulting changes to the national system. The team's plans to make the National Perinatal Survey data for 2003 and 2010 publically available will provide a very valuable resource to other research groups and policy-makers.

The research activities of the team that are focussed on the evaluation of the organization of and clinical practices in perinatal health care, particularly the influence of recent changes in the health care system (e.g. the cuts in the number of obstetric units in France) are of key importance given current stringent health care budgets and the economic downturn. Very importantly, the team has achieved two international patents in the field of predictive medicine, namely dealing with diagnostic strategies for acute meningitis and for vesico-ureteral reflux. Such an achievement is rare in the field of epidemiology.

Team members are active in groups developing clinical guidelines and participate in expert groups, boards of health agencies and professional societies, including some senior positions. There is considerable public and media interest in the topic of maternal and perinatal health and team members are accustomed to discussing their research activities and findings with the media (mostly in France, but with some international media work). Other public engagement activities include the activities within the Premup Foundation, which includes parents of preterm infants, together with contributions to books aimed at the lay public.

Assessment of the unit's organisation and life

Overall, there has been a clear scientific strategy for the work of the team over the past 5 years. The programme of work has recently been re-organised, with the identification of 5 themes, with each theme having two leaders responsible for oversight and management of research activity within their theme. There is strong evidence of an excellent organisation and governance in team 1, together with recognition by the leadership of the need for strong governance structures. The team's steering committee (laboratory committee) includes the director and director-designate, theme leaders and representatives of researchers, technical staff and administrators.

Interviews with a range of team members, including students, researchers and technicians, all endorsed the experts' impression of a very strong and effective leadership, excellent communication on all levels, and an excellent collegial atmosphere among the whole team. There is a strong affiliation of all employees to the team, and a high degree of engagement in the work of the team. Employees feel happy and comfortable and they are proud to be a member of team 1.

As stated, there is an excellent internal communication strategy within the team, as evidenced by the fortnightly team meetings (combining both administrative and scientific elements) together with regular meetings on financial/administrative management and laboratory council meetings. The new premises at Port-Royal provide a first-rate environment for the team, and the co-location of those working in Hotel Dieu Hospital appears to be working satisfactorily.

The successful grant applications to the European Union (EU) and on-going coordination of the European research projects underscores the high level of organisation within the unit, as management of EU funded projects is a complex and time-consuming task. This is in addition to the administrative burden of the numerous smaller grants active within the team. The appointment of a research coordinator in 2010 has no doubt contributed to the smooth running of the large number of projects within the team.

Presentations of the candidate director of team 1 and team members were well structured, rich in content, and very well presented. There appears to be a good relationship between the current director and the director-designate, which bodes well for the leadership transition. Interviews with the director-designate underlined substantial leadership potential, his outstanding vision, and his engagement for the new centre, and especially, with his team.

Assessment of the unit's involvement in training through research

There is a very strong engagement in academic and professional training within the team. Master's and doctoral students form an important and integral part of the team. On average, 2 new PhD and 8 Master students join the team per year. Team members are closely involved in the teaching of two Masters in Public Health, acting as co-directors of the Epidemiology track in both cases. There are 13 members of the team with accreditation to supervise postgraduate research (HDR). More than three dissertations per year have been defended during the past five years and more than 10 dissertations are under way at the moment. The students contribute to the excellent publication track record of the team. There is good supervision of the students, with regular meetings with their thesis supervisor and a programme of generic research skills training within the graduate school. PhD students are given the opportunity to (and encouraged to) attend and present at conferences. It is noteworthy, that several current researchers in the team were previously postdoctoral fellows in the unit, underlining the excellent atmosphere and academic attraction of this team. Senior team members play an important role in speciality training in obstetrics and paediatrics, and contribute to continuing medical education (CME) activities.

Assessment of the five-year plan and strategy

There is a clear and appropriate strategy regarding the five-year research plan of the perinatal, obstetric and paediatric epidemiology team. A key strength of the team is the solid foundation of perinatal epidemiological research over many years, which has allowed the generation of new hypotheses and identification of pertinent and important scientific questions. Thus, new projects have emerged from the earlier research period and are based on a large amount of experience and knowledge about the issues in question.

The reorganisation of the team has brought together researchers with expertise in clinical epidemiology and organization of care / health services research with those whose research is centred on causes of adverse perinatal events, and long-term outcomes of these. The rationale for introducing 5 research themes in order to increase synergies between projects and to add value to on-going and future work is appropriate; an example includes the proposal for a new project on preterm delivery and congenital heart disease, which draws on two established studies (EPICARD and EPIPAGE 2).

The strategy of developing clinical epidemiology in paediatrics in response to an identified gap in national research is also sound, but at present, Theme 5 (dealing with clinical epidemiology of routine practice in paediatrics) stands out as the weakest theme within the project. Although the content of research in themes 1-4 is coherent and has emerged based on prior expertise and existing large population-based studies and surveys, theme 5 has a poorer "fit" within the proposed project as a whole. The seven studies within theme 5 have limited inter-connectedness and it is difficult to see where the synergies with the other themes would be. The importance of addressing the need for paediatric clinical epidemiology in France is recognised, but it is recommended that the opportunity is taken to increase the coherence of research across all 5 themes – for instance by studying paediatric care of children of interest within studies in the other themes, e.g. children with neural tube defects or those with congenital heart defects, both groups requiring comprehensive and interdisciplinary care during childhood.

The potential of the research agenda is outstanding, given the established international and national networks on which it is based and the on-going long-term studies that are already in place and funded. In particular, the current leadership and/or participation in European research networks places the team in a strong position for leveraging future European research funding and indicates the team's capacity to play an important role in international perinatal and paediatric epidemiological research in the future.

The 5 year plan includes the strategy of developing new research projects that capitalize on the birth cohort research platform, including the collection of biomarkers. The on-going sub-studies based on the EPIPAGE2 (investigating the development small gestational age), such as EPIFLORE (investigating the development of the intestinal microbiota) and BIOPAG (early biomarkers of disease in very preterm babies) highlight the feasibility of this approach. Such a strategy is important given current interest in human host and microbiome interactions for health and disease.

Some consideration was given to the perceived benefits and added value of the proposed Epidemiology and Biostatistics Research Centre to the team and their contribution to the Centre, (e.g. contribution of datasets for use in developing methodologies; access to experts in complex statistical and epidemiological techniques), there is potential that the opportunities of the Centre will not be fully exploited. It will therefore be important to develop specific research projects with the other teams. An example could be to develop a study with the Clinical Nutrition team based on data on the prevalent and incident pregnancies in the Nutrition e-cohort.

Conclusion

- Strengths and opportunities:

Team 1 is a very strong and successful team addressing research questions that are important to public health, and with considerable potential for impact on future health and health policy. Their research focus will gain even more importance in the future given current and likely future societal and economic developments in Europe. Perinatal and paediatric clinical epidemiology is of utmost importance not only to understand better the reasons for adverse perinatal events, and thus to identify interventions for prevention, but also to ensure preservation of achieved quality in medical care.

Strengths of the team include their track record of obtaining research funding from a range of sources, including European Union, of successfully managing very large research projects and of establishing well-functioning clinical networks. The RE-CON-AI platform of birth cohorts provides an excellent opportunity for future work, as does the close association with the "Departement Hospitalo-Universitaire" (DHU) "Risks and Pregnancy", with the clinical expertise of the team a key strength. It is critical for clinical epidemiology to have such representation / links in order to identify pertinent or emerging clinical questions. There are considerable opportunities for developing innovative and truly multidisciplinary studies of international importance with the establishment of the Epidemiology and Biostatistics Research Centre.

- Weaknesses and threats:

Even though the expert team strongly believes that the proposed new research centre provides more opportunities than risks, there are some potential threats including some loss of autonomy within the team (depending on the leadership of the centre) and an attendant weakening of the team's research energies. Potential for redistribution of financial and personal resources across the different teams within the proposed centre might influence the performance of the individual teams.

Theme 5 of team 1 might remain some kind of appendix without real attachment to the research focus visible throughout and across the other 4 themes.

Several senior members of the team have to manage clinical, research and teaching duties, and a threat is that research results will not be delivered in a timely manner due to these competing duties.

The deficit of human resources with respect to the administration of large and complex research grants (such as those from the EU) might represent a threat to obtaining future EU research funding.

- Recommendations:

The management and maintenance of the large number of databases currently in the portfolio of the team 1 is both time and resource consuming. It would therefore be desirable to adopt the "COUNT" approach (i.e. Collect Once Use Numerous Times) when it comes to new data collection.

Theme 5 of team 1 should become a more integral part of the whole team 1 by investigating research questions affiliated to other cohorts studied in themes 1-4.

More efforts could be made to study influences of inequalities among minorities, socially disadvantaged populations and of migrants, and to collaborate with groups with expertise in such issues.

The team is multidisciplinary, but the disciplines represented are largely limited to different clinical specialties, epidemiologists and statisticians. The joint projects with microbiologists, genetics or other laboratory ('basic') scientists remain relatively small-scale and few in number. This is an area that could be developed over the next 5 years, particularly with respect to the potential for collection of samples / biobanks.

The team could consider developing new partnerships with health economists or social scientists over the next 5 years. For example, some of the health services research would be strengthened by a health economics element, whilst there would be potential in the future to carry out research with the school-aged children with congenital heart abnormalities on quality of life.

Team 2: Biostatistics and Clinical Epidemiology

Name of team leader: Ms Sylvie CHEVRET

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	5	8	8
N2: Permanent EPST or EPIC researchers and similar positions	2	2	2
N3: Other permanent staff (without research duties)	1	1	1
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)			
N6: Other contractual staff (without research duties)	11	11	3
TOTAL N1 to N6	19	22	14

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	0	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	6	9

• Detailed assessments

Assessment of scientific quality and outputs

The team is mainly involved in the study, development and applications of statistical methods for clinical research. In this domain, the team reached a very high level of expertise thanks to an active collaboration between biostatisticians and clinicians both within and outside of the team. The members have published 307 articles in peer-reviewed international journal since 2007, including many papers in high level medical journals. For about 90 papers, the team was the leader of the work (the 1st or last author was a member of the team) (N Eng J Med, Chest, Clin Infect Dis, Crit Care Med, Intensive Med Care, Bone Marrow Transplantation, Blood, Am J Respir Crit Care Med, J Clin Epidemiol …) but the team's members have also demonstrated their abilities to develop high level collaborations with an impressive number of collaborative papers in various medical domains. On both point of view (papers as leader and collaborative papers), this is an excellent level of publication reported to the size of the team.

Regarding their main field of research, methodology in biostatistics, the level of publication is not as high. Members of the team published 22 methodological papers over the 5 last years including 12 published in journals of biostatistics (only 5 papers in the top 20% journals of the speciality) and 10 in high level journals devoted to epidemiology or clinical trials. They published a book in 2006 about "Statistical Methods for dose-finding experiment" and are currently writing a book on "Statistical methods on ICU data" and a chapter in another book.

The main results in the past period concern flexible designs for phase I/II trials, Bayesian approaches for estimating treatment effect, propensity score approaches for non-randomized studies, joint models for longitudinal data and competing risks, measures of discrimination, multiple imputation and tools for monitoring quality and performance.

Assessment of the unit's academic reputation and appeal

The team welcomed 2 visiting researchers from foreign countries in the past five year periods and has developed several international collaborations with top-level biostatisticians (Cambridge, Columbia, Berkeley). Members of the team are involved in many national and international collaborative clinical projects.

One member is editor of the Intensive Care Medicine Journal.

Assessment of the unit's interaction with the social, economic and cultural environment

Most of the methods developed by the team are applied to clinical trials or epidemiological studies and members are involved in the design and analyses of many clinical projects allowing rapid transfer of their methodological results toward implementation of clinical trials. This is a major strength of the team and this is demonstrated by the impressive number of collaborative papers. It is rare that teams of research in biostatistics perform both original methodological developments together with so many high level clinical collaborations. The collaboration between biostatisticians and clinicians is permanent in this team.

Assessment of the unit's organisation and life

The management is adapted to the size of the team. The team obtained several grants from national funding agencies. A good support is given to the Master and PhD students. All the PhD students are funded. They attend international conferences at least once a year and attend training courses as recommended by their doctoral school. They have as many meetings with their advisors as they need (generally once a week) and are well motivated by possible new collaborations between teams within a research centre. One researcher of the team is in charge of advising them. Clear rules for authorship have been adopted and students most often sign the papers in first, including M2 students.

All the team's members are invited to attend a scientific meeting organised twice a month.

Assessment of the unit's involvement in training through research

Team's members are highly involved in teaching and training through research. Since 2007, 15 doctoral students have been welcomed and 6 have defended their thesis (no dropout). About 2 M2 students are welcomed each year.

The team 2 leader is the coordinator of a Master2 of Public health speciality "Methods in treatment evaluation" and is in charge of 1 training unit in another master. The team proposed a project of full master degree (M1 and M2) for 2014 with 6 second-year specialities. One member was director of the Doctoral School ED393 for Paris Diderot.

Assessment of the five-year plan and strategy

The five-year project is well justified, well structured, mostly in the continuity of previous themes of the past period (in which the team has developed high expertise) and concerns very competitive topics in biostatistics. It is organised around 3 main themes. The main one regards "innovative Bayesian approaches for clinical research" which is the main domain of expertise of the team. Several original and useful developments are planned in this field: online computer based tool for eliciting expert opinion, Bayesian adaptive allocation methods for patients in adaptive trials, new design for phase II screening trials and Bayesian method for medical-decision in collaboration with a researcher from team 4 in the project of research centre. The second theme about causal inference is less ambitious than the first one in terms of innovative methods. It is in two parts: (i) comparison of selection criteria for propensity score models and comparison of different procedures for multiple imputations in the context of propensity score modelling and (ii) comparison and application of the Targeted Maximum Likelihood and other methods of causal inference (collaboration with Berkeley, USA). The last project regards methods for prognostic modelling and includes innovative developments about imputation methods for competing risks and clustered data (collaboration with Cambridge) and development of prognostic models with time-dependent covariate.

Conclusion

- Strengths and opportunities:

The main strength of this team is its involvement in clinical research allowing permanent interaction between biostatisticians and clinicians and rapid transfer of new methods to the application. This makes possible the development of innovative methods extremely useful in clinical research.

If the research centre was created, this would be a great opportunity for new collaborations. This could lead to the development of new themes of research in biostatistics with direct applications to very large and extremely rich cohorts.

- Weaknesses and threats:

Although 2 researchers plan to pass their HDR in the next year, increasing to 4 the number of researchers able to advise PhD students in biostatistics, the main difficulty is linked to the small size of the unit relatively to the overall centre. After the departure of two researchers in biostatistics during the past period (one moved to another team within the project of research centre and continue to collaborate with the team's members), the team is currently composed of 8 clinicians and only 4 tenured researcher in Biostatistics including 1 retired researcher (emeritus) and 1 INSERM researcher who began only recently a research activity in Biostatistics after a complete change of domain of research.

- Recommendations:

To take full advantage of the opportunities of the collaborations within the research centre, it would seem appropriate to reinforce the critical mass of biostatisticians in this team and therefore to train young researchers able to apply for permanent positions. An alternative that should be discussed with the other teams would be to help to develop the statistical skills within teams that are in demand (mainly team 1 and 3). In this last scenario Team 2 could serve as a reference for statistics (training, expertise, validation of methods …) for the centre.

Exchanges and international collaborations with biostatistician should be pursued. Methodological developments could be submitted more frequently to highest level biostatistical journals.

On the other hand, clinicians of the team also have an excellent level of publications in clinical research. Most of these projects take advantage of the methodological development of the team but they pursue their own goals. Maybe these clinical projects could appear per se among the team's projects of research and not only as application of the methodological development.

Team 3: Nutritional Epidemiology

Name of team leader: Mr Serge HERCBERG

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	14	15	15
N2: Permanent EPST or EPIC researchers and similar positions	9	9	9
N3: Other permanent staff (without research duties)	14	15	2
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	4	4
N6: Other contractual staff (without research duties)	26	27	
TOTAL N1 to N6	66	70	30

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	10	
Theses defended	9	
Postdoctoral students having spent at least 12 months in the unit	8	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	10	11

• Detailed assessments

Assessment of scientific quality and outputs

The Team 3 has an impressive scientific production with a high number of papers in international journals in the scientific field of good to very good quality, also in the 5% best journals of the speciality. Over the 6 years there is an increase in the scientific production and in the higher rated journals. Specifically:

-186 articles within the team 3 research activities (mean IF: 3.79) most of them in 1st, 2nd or last position including 1 Ann Int Med, 2 Arch Int Med, 1 BMJ, 1 Lancet Oncol, 1 Canadian Medical Association Journal , 16 American Journal of Clinical Nutrition, 2 J Lip Res, 1 Diabetes Care and 2 Obes Rev and varying in number and quality according to the team (66 papers of mean IF 4.47 for theme 1; 34 papers of mean IF 4.16 for theme 2; 8 papers of mean IF 3.33 including for theme 3; 78 papers of mean IF 3.10 for theme 4);

-140 articles of very high quality in collaborative works (mean IF: 6.09) including 1 Nature, 11 Nature Genet and 1 Journal of the American College of Cardiology, generally with unit members in intermediate position of authorship;

- >78 papers in French journals.

Many invited conferences (82) and oral communications (60) in national and international meetings and congresses.

Assessment of the unit's academic reputation and appeal

The researchers have a long-lasting reputation in the international scientific field. In the last 5 years they have been involved in 6 European and international projects (in charge of work-packages).

The team 3 is leader of 2 ANR projects and participates in several collaborative national projects including “Invest for the Future” projects (Open Food system and Labex Milieu interieur).

Several team members have an internationally and nationally recognized expertise in the field of nutrition, obesity and physical activity with a leader position or responsibilities in research groups and networks (National Program Nutrition-Santé, Nacre, European association for the study of obesity, World Cancer Research Fund…). They are regularly invited in international meetings.

The team has developed long-term or more recent collaborations with international laboratories (London Imperial College, Oxford University, London School of Hygiene and Tropical Medicine, US-National Cancer Institute, Leeds University…) and with many French laboratories.

Relatively few foreign postdoctoral students or visitors have been hosted in the team in the past years.

The national recognition of the scientific expertise of some unit members is attested by their participation into committees of national agencies (Institut national de prévention et d'éducation pour la santé [Inpes], Institut National du Cancer [Inca], Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail [ANSES], AERES evaluation committees, specialized scientific commission of INRA for example.

Assessment of the unit's interaction with the social, economic and cultural environment

The team has a strong interaction with the social environment, collaborating with public health policy makers in order that citizens get to know about research results. This is demonstrated by numerous articles for professional or technical journals over the past five years (69), as well as the production of numerous reports useful for policy makers and for the setting up of guidelines.

The team made a great effort for disseminating scientific culture in the field of nutrition in extra-academic settings via numerous interviews, conference exhibitions towards professionals or general population.

The team has largely demonstrated its ability to obtain contracts from private companies (Mederic, Pierre Fabre, GlaxoSmithKline), to develop a partnership with the Joint technical network “Sensorialis” for the project EPIPREF (Centre of Taste Sciences and Alimentation , Dijon) and more generally, has a highly successful to raise funds.

Another strength of the team was to introduce new web-based instruments in epidemiological cohorts and to make efforts to disseminate this tool in the national and international epidemiological community (close contacts with German, English and US teams).

Assessment of the unit's organisation and life

The team has currently 66 collaborative members. Their project includes a modification of the internal structure to one single team working on 4 main themes in order to reinforce the interactions between the four groups.

There is a very well organized internal management structure, with regular team meetings concerning both the internal and the external aspects of research and other day-to-day issues. The administrative staff on a full-time equivalent is important for the organisation and is seen as a strength.

In the last years, the team, under the governance of its leader, demonstrated its capacity to recruit young researchers and to obtain permanent positions for many of them either as INSERM research fellows or as university assistant professors. Even if some staff members (both researchers and engineers/technicians) joined the team relatively recently, there are clearly close connections between them. The intranet system has been mentioned by several team members as a very efficient way of making the information circulate and is easy to use. The team is very well organized with regard to sharing resources (cohorts, computing facilities, food composition tables, biobank…).

The internet website is very informative and regularly updated as checked by the members of the evaluation committee.

Assessment of the unit's involvement in training through research

The team has a strong involvement in training modules in the field of nutrition and health and published book chapters for training in nutrition with a national diffusion. Particularly, it designed and coordinates the Human nutrition and public health Master 2 programme Paris 13 (since 2009) which largely contributes to its attractiveness.

The team also coordinates the module nutrition and public health of the Master 1 programme (Paris 13) and participates in other Master programmes in Paris 13 and other universities (Paris 5, 6, 7).

Many students of masters 1 and 2 (20), and PhD students (18 of whom 10 defended during the preceding contract) have been hosted in the team which developed a very efficient coaching of PhD students (meeting on a bi-weekly basis with trained advisor, manual of guidance…).

There were 9 postdoctoral students during the last contract, 3 mentioned in the future contract including one foreigner. There is no mention of participation in international training networks.

Assessment of the five-year plan and strategy

The team plans to examine a wide range of nutrition–related issues with a high potential for improving nutritional recommendations and thus for contributing to primary or secondary prevention strategies in the population.

The team has access to an impressive platform of databases derived from existing or ongoing cross-sectional and cohort studies (either randomized trials or observational studies) including the Nutrinet-Santé Study, generally coupled with well-organized biobanks. Despite the know-how of the team, there are, however, some concerns about the achievement of initial recruitment objectives (300 000 “true” participants) for the Nutrinet study due its funding uncertainty.

The team plans to develop new research topics some of them being ambitious and innovative, like the introduction of web-based tools in large scale cohorts for reducing the costs and improving data management processes, the development of new tools in innovative research fields (such as the sensory and cognitive determinants of dietary and eating behaviours) or new instruments for assessing physical activity. The committee was however concerned by the risk of scattering of the internal forces with novel topics relating nutrition to cognition, chronic inflammatory diseases or reproduction disorders that may be promising but there are subjects to some uncertainties about the adequacy of tools (cohort, study design, staff) in some instances (multiple sclerosis, reproduction…).

Some scientific objectives (for example, the relationships of polyphenols, vitamin D, or weight change, with cancer or cardiovascular and metabolic diseases) appear more traditional and in strong competition with other groups at the national and international levels. In many cancer-related sub-projects, considering cancer as an overall entity is conceptually questionable in view of the large differences between site-specific cancers both in risk factors and in cancer biology. Cancer-site specific approach is mandatory but implies a risk of long-term responses (to be expand beyond the next contract).

There is a good synergy between the various research axes which benefit from the long lasting team experience in nutrition and related fields (obesity and physical activity) and from the very good knowledge of the national and international environment in this field. The team has demonstrated its ability to establish appropriate national and international collaborations, including collaborations in other research fields (for example centre of sensory taste in Dijon, teams specialized in humanities and social sciences or in quality of life) in order to achieve its objectives.

Conclusion

- Strengths and opportunities:

The team lead by Mr Serge HERCBERG has an excellent reputation in the field of nutritional epidemiology. There is a solid transfer of knowledge to the scientific community, to policy makers and to the consumers. One of the main strengths is the number of researchers involved in the group and the scientific production. The website is also seen as strength.

The team has set up a large number of cohorts, some of them still in their follow-up phase.

The inclusion in the PRES centre is seen as a good opportunity to upgrade their methods in terms of analysis, and thus to be able to publish in higher ranking medical journals. For the PRES, the inclusion of the Mr Serge HERCBERG team will be a clear asset in order to include nutritional aspects in the other research lines as well as sharing resources expertise (cohorts, biobank,…) with other teams.

The combination of large biobanks with clinical databases is a major strength and offers opportunities for active collaborations with other groups at the national and international levels.

The new e-cohort is an opportunity to have access to many data and to share with other research groups with complementary expertise.

- Weaknesses and threats:

Nutrition as a science has turned in the last years into a multidisciplinary science, as it has been linked with both communicable and non-communicable diseases. A common threat for research teams working on nutrition (in this case nutritional epidemiology) is to broaden too much the research areas. The strategic plan of the group should take into account this aspect and establish strong research priorities.

Funding for the NutriNet Santé Project doesn't seem to be secured – particularly the analysis of the blood samples.

To date, projects of scientific interactions with other teams of the Centre seem rather limited.

Mr Serge HERCBERG will be retired at the end of the next term (2018) but discussions about a future leader of the team have already started.

- Recommendations:

The participation in international training programs could be a target in the future in order to improve international collaborations and the exchange of researchers.

The team should be proactive for cross-cutting research exchanges on nutrition with other teams within the Centre. There seems to exist a short-term opportunity to study nutrition during gestation (Team 1).

The team should increase its expertise in novel statistical methods as well as in physical activity and sport sciences as it is an important emerging topic in the group (Team 2). As nutrition is more and more integrated in the lifestyle concept, the physical activity part should grow in the next years and probably will need some reinforcement.

The team should more clearly define research priorities in order to focus on innovative fields with high probability of outstanding publications, and develop an appropriate strategy for setting up projects with the other teams of the Centre.

The committee recommends to pursue the discussions and coaching for a future leader of the team.

Team 4: Clinical Epidemiology applied to osteo-articular diseases

Name of team leader: Mr Serge POIRAUDEAU

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	8	8	8
N2: Permanent EPST or EPIC researchers and similar positions			
N3: Other permanent staff (without research duties)	1	1	1
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)			
N6: Other contractual staff (without research duties)	2	2	2
TOTAL N1 to N6	11	11	11

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	8	9

• Detailed assessments

Assessment of scientific quality and outputs

There has been a high volume of publications in peer-review journals: 505 over 2007-2012, and increasing productivity with 97 articles published in 2012 (106 are listed in the document but at least 9 are listed twice).

Many articles are published in the best journals in the field with high impact factors, for instance in 2012 approximately 40 papers were published in journals with IF between 4 and 8, and 10 papers in journals between >8 and 10. One paper was published in first position in 2009 in the Ann Intern Med (IF 16.7) and one paper in first position in J Clin Oncol (IF 18.37) in 2011. One paper as collaborator was published in the Lancet (2009).

To be noted, some papers are on innovations in statistical tools applied to learning curves and quality of care assessment including one published in Stat in Med. This work has been conducted in collaboration with team 2 and could have a significant impact on the scientific and clinical environment.

Some papers carry very interesting and original ideas on management of osteoarticular diseases, clinical epidemiology in musculo-skeletal diseases, and access to large national and international cohorts.

Team members have coordinated several international trials in rheumatoid arthritis, have obtained several PHRC grants to conduct national trials and cohort studies, and are part of the steering committee of an European study: GLOW.

International and national visibility is clear for the rheumatologic and rehabilitation teams. National visibility identified for the radiologist team.

Assessment of the unit's academic reputation and appeal

The group, especially the rheumatology and rehabilitation teams, are involved in several national and international collaborative research projects and networks, and numerous collaborations with other research teams.

The unit has received the label from the European League Against Rheumatism (EULAR) and the European Ligue of Rehab medicine) and is a EULAR centre of excellence.

Team members are part of the steering committee of two cohorts of patients ESPOIR and DESIR. One of the members of the team (MD) is the principal investigator of the DESIR cohort.

The team has strong implication in the international initiative OMERACT (Outcome Measures in Rheumatology).

Assessment of the unit's interaction with the social, economic and cultural environment

Members of the team are involved in steering committees and scientific or academic boards and often at a high level: presidency of the GRIO (French National Group for research against Osteoporosis); presidency of the national college of rheumatologists; presidency of the European League Against Rheumatism (EULAR); presidency of the French college of professors in Rheumatology; vice-presidency of the ASA (Assessment of Ankylosing spondylitis); presidency of the EULAR standing committee for treatment of knee Osteo-Arthritis.

The team leader is currently vice-president of the French Society for rehabilitation medicine, he is also vice director of the “Institut Fédératif de Recherche Handicap” (INSERM/CNRS), member of the national college of professors in rehab medicine, vice-dean for the students life of medical school of Paris Descartes.

Team members strongly contribute to the writing of national guidelines in the field of osteoarticular diseases. They also significantly contribute to the dissemination of scientific culture, continuing education and public debate (e.g. a series of documents regarding disease in 100 questions: osteoarthritis, rheumatoid arthritis, spondylitis, low back pain…), the guide of back pain, and a number of documents regarding osteoporosis prevention. They participate to patients’ associations.

Team members are involved in Editorial boards of several journals: Annals of the Rheumatism diseases, Arthritis and Rheumatism, Osteoporosis International, journal European Radiology.

They have collaborations with Ecole Nationale des Arts et Métiers (ENSAM, a University for engineers) (MRI and TDM), with department of social sciences of the university (UFR SHS Paris Descartes), NEUROSPIN for development of new technologies in MRI.

They are occasionally experts for the HAS; and coordinator of several reference centres (sarcomas, rare bone diseases…).

Assessment of the unit's organisation and life

There are regular meetings with rheumatologists, orthopaedic surgeons, rehab physicians, and radiologists. They are in very close buildings and are used to work together in the clinical setting.

The team is composed of 14 members. 8 are permanent staff with academic position: 6 PU-PH and 2 MCU-PH, they all have HDR. 2 are permanent hospital staff with no academic position but a strong involvement in clinical research and responsibilities in conducting research projects and publications, one has a HDR; 2 other members are doctoral fellows, and 2 are MD's under contract with full-time activity in research.

Most members of the unit are clinicians with only two members having a formal training in epidemiology/biostatistics. To date, no formal organisation exists overall. It is planned to implement a directing committee composed of the leader of each of the three themes developed by the team.

Assessment of the unit's involvement in training through research

More than 30 residents from foreign countries have been received during the period 2007-2012, but presence of Master's degree trainees (M1 and M2) and doctoral students received is not mentioned.

Involvement in national training for rheumatologists and radiologists, involvement in international training networks: European school of radiology, European Courses for fellows in physical medicine and rehabilitation.

There are currently three doctoral fellows in the team and no post-doc students.

Improving the training through research is planned although not precisely.

Assessment of the five-year plan and strategy

Three research themes have been identified: 1. The development of outcome criteria for musculo-skeletal diseases. 2. Analysis and evaluation of acquired disability due to musculo-skeletal diseases, and 3. Evaluation of complex interventions in the field of musculo-skeletal diseases. These themes are clearly appropriate within the national and international context and correspond to major issues regarding musculo-skeletal diseases. However, no clearly defined strategy emerges from the document and from the presentation. There is an obvious synergy of team projects, and a convincing general feasibility. It is planned to strengthen partnership already existing with social sciences and engineers.

Some sub-themes are original and innovative such as work on learning curve which has been developed in collaboration with team 2. Other original developments are being considered such as learning curves for low back pain patients that are promising. This sub-theme is part of theme 1 but the coherence of this is not straight forward; it could be envisaged to consider this topic is an individual theme. Other sub-themes are original such as patient-reported outcomes, although no collaborations are planned with other French teams working in the field.

Conclusion

● Strengths and opportunities:

High volume of publications in high IF journals, with respect to the discipline's standards.

Very good national and international reputation and visibility, international collaborations.

Strong potential to develop a research project on clinical epidemiology applied to rheumatic and musculoskeletal disorders.

Pluridisciplinary teams in the field of musculo-skeletal diseases, access to several national and international cohorts.

Ongoing collaborations with team 2 and team 5.

● Weaknesses and threats:

Lack of specific prospective strategy in terms of scientific agenda and in terms of team building.

Team based mostly on clinicians with no permanent epidemiological researcher.

Lack of implication in training in epidemiology / biostatistics.

● Recommendations:

Increase internal resources in epidemiology to supervise PhD students in clinical epidemiology.

Improve knowledge and collaborations with other French teams working in the field.

Clarify more precisely the strategy planned to improve training through research and the analysis of the usable skills and resources available and able to be deployed.

Need to develop the more specific research agenda focused on clinical epidemiology applied to rheumatic and musculoskeletal disorders, with a need of epidemiological coaching.

Team 5: Method of therapeutic evaluation Chronic diseases

Name of team leader: Mr Philippe RAVAUD

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	7	7	7
N2: Permanent EPST or EPIC researchers and similar positions	3	3	3
N3: Other permanent staff (without research duties)	2	2	1
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2	2
N6: Other contractual staff (without research duties)	6	6	4
TOTAL N1 to N6	20	20	17

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	13	
Theses defended	8	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	4	
Qualified research supervisors (with an HDR) or similar positions	6	6

• Detailed assessments

Assessment of scientific quality and outputs

The team has an outstanding scientific production in terms of both volume and ranking of original articles, which in several instances reach the highest international standards.

Within the past 5 years, this relatively small team had a very high scientific output of 457 peer reviewed publications. They had a leading position for 231 of these publications (1st, 2nd or last author) among which 93 were in the top 10% of speciality journals and 22 in top general medicine journal (NEJM (1), Lancet (2), JAMA (2), Ann Int Med (4), PlosMed (4), BMJ (7), Arch Int Med (2)). Eight papers were in the top 1% of cited papers according to the Web of Science.

The team is a leading reference in the field of meta-epidemiological studies, reporting standards and other important aspects of clinical epidemiology internationally. They contributed to a very innovative concept of “spins” in interpretation of results of clinical trials, other important work related to the emerging field of network meta-analysis.

Assessment of the unit's academic reputation and appeal

There is a very strong international recognition of the team. Several of its researchers are invited to communicate at leading international scientific meetings, and some high-level foreign researchers were recruited to work in the team.

The team is involved in leading CONSORT as a highly cited initiative on improving the standards of reporting of clinical trials - the next CONSORT meeting will be held in Paris in 2014 under their supervision. It is an internationally recognized leader in meta-epidemiological studies and several other methodological themes of the Cochrane Collaboration. Team members are part of the centre directors network and methods group networks of the Cochrane collaboration.

The team has well established and very effective international collaborations with Oxford University (one researcher working jointly for both teams, 10 papers with both institutions, 2 exchanges of researchers); with Department of epidemiology of Columbia University (two of the team members are respectively senior lecturer and associated professor in this institution and there are ongoing projects and exchange of students); other with other universities around the world (University of Ottawa (8 papers together), university of Copenhagen (5 papers), University of Bristol School of Social Medicine, and other leaders in the field.

The team has been very successful to raise grants (2.4 M€ since 2007) and has been nominated as "team hope for research" by the Fondation pour la Recherche Médicale which has very high standards.

Assessment of the unit's interaction with the social, economic and cultural environment

The team has a national and international recognized expertise in bias in clinical trials, quality of reporting, selective reporting of outcomes and research integrity. As such the team leader had important direct interactions with various administrative bodies (French National Assembly, European Commission’s Director of Health on access to clinical trial data, FDA Think-tank) as well as several Journal Editors (BMJ, Ann Int Med, invitation to participate to the international congress on peer review).

At another level, the team has strong interactions with network of clinicians as well as researchers and is currently developing a website of trials in health care for these communities. They are also developing a website for patients advocating the use of appropriate testing of treatments.

Assessment of the unit's organisation and life

The cohesion of the team seems excellent. There is a common understanding of scientific scope and culture within the team. There is an annual scientific meeting of the entire team and more regularly brainstorming meetings with senior, junior, and foreign researchers mainly from Oxford. Although there are regular weekly meetings, engineers and technicians seem to have had limited information and discussions about the project of centre. However, the leader appears to be able to manage conflicts and situation of transition nearly optimally.

Assessment of the unit's involvement in training through research

There is an excellent structured integration of MSc (8 to 10 per year) and PhD (3 to 4 new students per year) students in the scientific activities of the team, with many papers in leading medical journals published that emerged from MSc and PhD projects. Students are guided through their professional experience; there are regular meetings with supervisors. There are established strategies for close monitoring of PhD students who appear highly motivated.

The team is involved in high-level postgraduate courses and research seminars, nationally (direction of a Master in methods in therapeutic evaluation and they are launching a new master course in 2014 in English in comparative effectiveness research) and also internationally (involved in PhD programme, summer courses, and master of public health at Columbia University and Erasmus Mundus Masters programme).

Assessment of the five-year plan and strategy

The program is based on a clear strategic thinking about the complexity of therapeutic evaluation and communication on this evaluation. It is therefore ambitious and innovative and integrates some high risk – high benefit sub-projects. The "spin" approach is particularly innovative and potentially important for the medical research community at large.

The objectives could sometimes be more specific, the methods for stepwise achievements during the program need to be specified more in the near future. Some aspects of complex system approach need more maturation.

Overall, most of the project is clearly feasible with regard to resources and experience, and naturally builds on previous work on the team. The team has an excellent knowledge of the field, and has developed innovative concepts. The project is likely to contribute to the team's leading international position.

Conclusion

- Strengths and opportunities:
  - Outstanding scientific production;
  - Strong international recognition thanks to expertise and output, excellent international network;
  - Excellent cohesion of the team, very good communication internally and externally;
  - Very well established structure and processes for PhD students. Strong involvement in teaching and training;
  - Ambitious and innovative research program.
- Weaknesses and threats:
  - The objectives of the research program tend to be a bit unspecific and the methodology for the program became sometimes unclear during oral presentation and question and answer session.
- Recommendations:
  - To be more specific when defining the objectives of the proposed research program;
  - To develop cross-cutting research project with other teams (1 and 3 for example).

5 • Conduct of the visit

Visit dates

Start: 29th of January 2013, at 8:30 am

End: 30th of January 2013, at 6:00 pm

Conduct or programme of visit

Day one – January 29th 2013: Maternité Port-Royal

8:30	*Welcome (closed-door meeting): Visiting committee with the AERES scientific advisor*
9:15	*Plenary session (salle 1)*
	***AERES representative**: the role and procedures of AERES*
9:30	***Director of the Unit, Mr Philippe RAVAUD (30' presentation, 15' discussion):** General strategy*
10:15	***Team 1 – Perinatal, Obstetric, and Pediatric Epidemiology** (30' talk + 25' discussion)*
	Mr Pierre-Yves ANCEL
11:10	*Coffee break (15')*
11:25	***Team 2 - Biostatistics and Clinical Epidemiology** (30' talk + 25' discussion)*
	Ms Sylvie CHEVRET
12:20	***Team 3 - Nutritional Epidemiology** (30' talk + 25' discussion)*
	Mr Serge HERCBERG
13:15	***Lunch** (6ème étage)*
14:15	***Team 4 - Clinical Epidemiology applied to osteo-articular diseases** (30' talk + 25' discussion)*
	Mr Serge POIRAUDEAU
15:10	***Team 5 - Method of therapeutic evaluation chronic diseases** (30' talk + 25' discussion)*
	Mr Philippe RAVAUD
16:05	*Coffee break*
16:20-18h00	*Debriefing closed-door visiting committee*

Day two – 30th of January 2013: Maternité Port-Royal

9:00	***Three parallel meetings with personnel without head, or team leaders***
	Discussions with engineers, technicians, administrative (salle 2)
	Discussions with staff scientists (salle 1)
	Discussions with students and post-docs (salle 3)
10:00	***Face-to-face meeting of the visiting committee with the head of each team**: 5*10'=50' (salle 1)*
10:50	*Coffee break*
11:05	*Discussion with the direction committee: head alone (20') + head and team leaders (30')*
11:55	*Discussion with the representatives of managing bodies without the direction committee (60')*
12:55	*Lunch, including representatives of managing bodies and the direction committee (60')*
13:55	***Private meeting of the visiting committee (in presence of the AERES scientific advisor)***
17:00	*End of the visit*

6 • Statistics by field: SVE on 10/06/2013

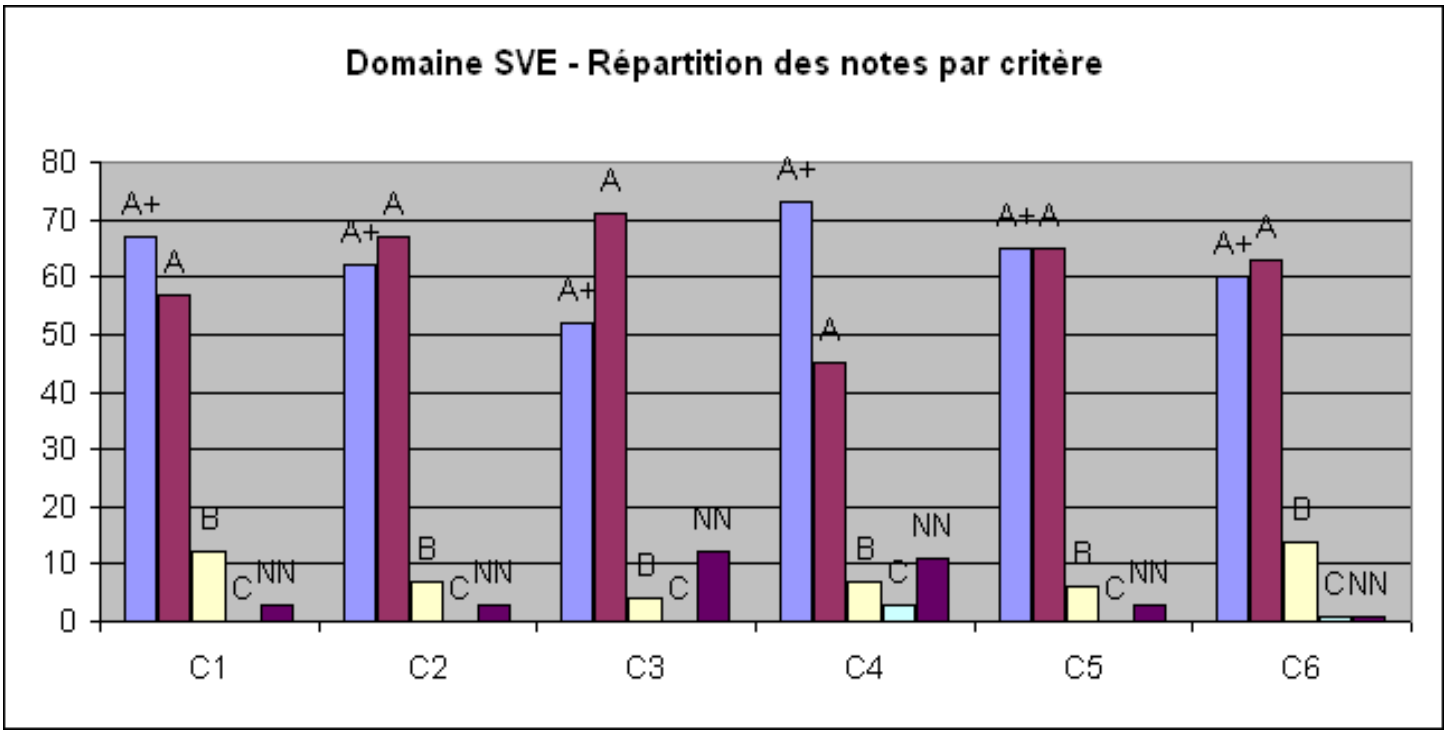
Grades

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	67	62	52	73	65	60
A	57	67	71	45	65	63
B	12	7	4	7	6	14
C	0	0	0	3	0	1
Non Noté	3	3	12	11	3	1

Percentages

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	48%	45%	37%	53%	47%	43%
A	41%	48%	51%	32%	47%	45%
B	9%	5%	3%	5%	4%	10%
C	0%	0%	0%	2%	0%	1%
Non Noté	2%	2%	9%	8%	2%	1%

Histogram



7 • Supervising bodies' general comments

UNIVERSITÉ PARIS DESCARTES

Vice Président du Conseil Scientifique

Paris le 15.04.2013

Vos ref : S2PUR140006296 –Centre de Recherche Epidémiologies et Biostatistique Sorbonne Paris Cité - 0751721N

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
Agence d'Evaluation de la Recherche et de l'Enseignement Supérieur
20, rue Vivienne
75002 PARIS

Monsieur le Directeur

Je vous adresse mes remerciements pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise concernant l'unité « Centre de Recherche Epidémiologie et Biostatistiques Sorbonne Paris Cité »

Vous trouverez ci-joint les réponses du Directeur de l'unité, Philippe RAVAUD.
Le Président et moi-même réaffirmons notre soutien total à ce nouveau projet que nous jugeons ambitieux et structurant pour l'ensemble de Sorbonne Paris Cité (SPC). Comme tout nouveau projet, du temps sera nécessaire pour l'optimisation des moyens et des ressources en fonction des ambitions affichées et nous sommes certains que nombre de commentaires du comité seront naturellement dépassés au cours du contrat. Dans ce contexte, les appels d'offre de SPC permettront des marges de manœuvre supplémentaires et importantes.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de ma considération distinguée.

Le Vice Président du Conseil Scientifique

Stefano Marullo, DM, DesSci

Université Paris Descartes, Vice-présidence du conseil scientifique, 12 rue de l'école de médecine, 75170 PARIS cedex 06
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AERES report on unit: Epidemiology and biostatistics Sorbonne Paris Cité

We thank the AERES expert committee for the on-site visit and the evaluation report. We acknowledge the quality of their work, the thorough and detailed evaluation. We appreciate their constructive comments and recommendations that we will endeavor to follow.

We would like to make some comments on the evaluation report. We include them as point-by-point responses regarding the assessment of the unit and the team-by-team analysis, respectively. When a "Recommendation" follows a "Weaknesses and threats" point, we answer both at the same time.

Assessment of the Center

- Weaknesses and threats: Projects of collaborations, sharing resources and infrastructure are still limited.
- Recommendations: To build a common strategy for developing and sharing research infrastructures such as biobanks and large databases.

We acknowledge that projects of collaborations were still limited at the time of writing the report. However, the number of collaborative projects has increased substantially since the report writing. In fact, at least 25 research projects involving researchers from at least 2 teams (and up to 4 teams) in the Research Center have been initiated since March 2012.

Contrary to most Research Centers in the field of Life Sciences, setting up the Research Center was not justified by sharing costly infrastructures. In fact, the research performed by the 5 teams does not require any expensive equipment with, consequently, no reason for infrastructure mutualization. The only exception is biobanking, and we explicitly pointed out that we were working on a strategy for sharing biobank resources. However, this is a complex issue because large-scale biobanks are created on sites hosting some of the teams and mutualization could be considered at the site-level as well.

Cohorts are sometimes considered research infrastructures because of the costs of setting-up and follow-up. The Research Center will definitely elaborate a common strategy for mutual organization of cohort studies. Nonetheless, most cohort studies of the Research Centre have already been funded and have been running well for several years. Thus, there would be no benefit in modifying, in the short-term, their efficient and successful organization. In contrast, new upcoming cohort studies (e.g., our e-cohort study on chronic diseases) is already benefiting from mutual expertise and shared resources (e.g., project manager).

If the large databases obtained through these cohorts are considered resources, we will certainly make it a rule to share data between teams within the Research Centre but also with external teams. A working group involving all the teams has already been created to collect information on all available databases, to describe their content in a standardized way, to specify their access conditions and to publicize this information to all the teams.

Regarding other resources (people and funding), most comes from grants (through Requests for Proposal), each dedicated to a specific project. Sharing resources in the short-term is thus only possible through joint resources obtained for the Research Center.

- Weaknesses and threats: Location on multiple sites is an issue which seems to have no short-term solutions.
- Recommendations: To reinforce and to innovate scientific animation in order to overcome the limitation of multiple sites; partial grouping of forces and setting up of common premises at the Hotel-Dieu could also help in that matter.

In fact, it is impossible in the short-term to put together on a single site the 4500 m^2 we currently have for the 5 teams. However, the situation has improved for some teams. Team 1 was historically located on 3 different sites and is moving to 2 nearby sites. We fully agree with the recommendation regarding the grouping of some of the forces and the importance of having common premises at Hotel-Dieu. The latest information obtained about our location at Hotel-Dieu is

favorable. Professor Andre Syrota, CEO of INSERM, supports the localization of the Research Center at Hotel-Dieu. In the short-term (late 2013 or early 2014), at least 3 of the 5 teams are expected to have their own offices at Hotel-Dieu. We should also obtain common premises for the Research Center: offices for teams not located at Hotel-Dieu and our administrative team, common meeting rooms of various sizes. Discussions are under way with the precursor of the Hotel-Dieu Public Health project for these additional premises.

We are fully convinced that the scientific animation is actually crucial to the success of this project. We therefore set up a very comprehensive and ambitious animation program with a mix of conventional (e.g., specific courses on "Critical Thinking Skills", critical analysis of protocol or project, journal club in English, mentoring with statistical support and in-house peer review for the first grant application) and highly innovative methods (e.g., research "speed dating," which allows center researchers to come together to discuss their research interests and find others with ideas or expertise they can draw on). We are therefore surprised by that recommendation.

- Weaknesses and threats: The scientific strategy of the centre and particularly the interactions between teams is not matured enough. Only few common cross-cutting projects have been envisaged so far.

Our claimed strategic choice was to discard a top-down approach to the scientific project, which seemed artificial, ineffective or even dangerous for adherence of researchers to the concept of Center. This strategy could explain why experts felt that our scientific strategy was insufficiently matured. This choice was clearly dictated by our knowledge of our national and regional environment, the diversity of cultures and histories of the constituent teams as well as the personalities and statutes of our researchers, but also by our concept of research. Therefore, our choice was clearly to favor a "bottom-up" approach for the emergence of joint scientific projects (in accordance with the recommendation of the experts). The adherence of researchers to the project, which was noted by the expert committee during its meeting with 70 researchers from the Center, and the emergence of almost 25 collaborative projects (with interactions between 2 to 4 teams for each) within 1 year are for us the best proof that this strategy was good (at least in our research context).

- Weaknesses and threats: Most teams have experienced difficulties attracting foreign researchers, particularly post-doc students.
- Recommendations: To improve attractiveness toward foreign researchers and post-doc students by joining means and forces.

This problem seems common to many French teams. In fact, we have not experienced difficulties in attracting researchers. However, when researchers or post-doc students want to join us, we are faced with multiple practical problems, which makes our teams unattractive or uncompetitive (e.g., unresponsive administration, complex procedures, insufficient hardware support, high cost of housing in Paris). We will try to improve our "material" attractiveness, which is currently poor, in connection with the PRES Sorbonne Paris Cité.

- Recommendations: To carry on in depth discussions in order to have an appropriate strategy to set up and develop the centre for the next 5 years. This could include to encourage bottom-up cross-cutting projects between teams which are essential for building the centre. Common projects should be encouraged as a first and foremost goal of the centre and should be supported by dedicated means coming from or raised by the various teams.

We have had this in-depth discussion regarding the strategy to set up the Research Center for several months. Our primary objective for the Center is that the scientific production (both in terms of quality and quantity) will be greater than the sum of the scientific productions of the 5 constituent teams if they remain isolated. We are convinced that bottom-up cross-cutting projects are one way to achieve this goal. However, we also believe that other methods (sharing of different methods, data, expertise and technicalities, sharing of different ways of thinking, benchmarking the teams regarding their mode of organization or working) are at least as important for achieving this goal.

To initiate collaborative projects, members of the management team of the Center (who now have good knowledge of the skills of most researchers in the center) are already systematically offering

researchers of their team to associate members of other teams with their project when appropriate. This strengthens the interaction between researchers of different teams and could improve the quality of these projects through the collaboration of different expertise and scientific cultures.

From our point of view, it is unrealistic, in view of the expected funding of the Center, to imagine developing new ambitious collaborative research projects with our own resources. However, the existence of Grant Requests for Proposals from the PRES seems an excellent opportunity to develop these projects. For instance, several teams will jointly respond to the Interdisciplinary Programs Call by the PRES Sorbonne Paris Cité in May 2013.

- Recommendations: To implement a policy to encourage the emergence of: 1) new teams and in particular teams of clinicians in various specialties, probably after an incubation phase within a larger team of epidemiologists 2) future leaders within the teams.

We are completely favorable to encourage the emergence of new teams, including teams of clinicians. However, we want these teams to have an interest and expertise in the field of epidemiology (especially, clinical epidemiology). For this five-year contract, we chose to propose the emergence of a team in clinical epidemiology applied to rheumatic diseases (after a long selection process). This team seems to have the most promising scientific potential. It has already a high-level scientific research production, although it is not an official research team. Moreover, its clinical academic staff has extensive experience in methodology and clinical epidemiology (one of its orthopedist surgeon is publishing in *Statistics in Medicine* as a first author) and has strong interactions with the 2 methodological teams of the Research Center (teams 2 and 5). We have already identified other teams that could emerge in the long term and are already incubating in some teams of the Research Center.

Moreover, we pay particular attention to the emergence of potential future leaders of teams or of the Research Center. As the committee could see, potential leaders do exist and the situation is in safe hands for all teams. We bring special attention to strengthen the emergence of these future leaders by involving them gradually in all discussions, decisions, drafting documents, contact with decision-makers, participation in committees and training in scientific staff management or recruitment (e.g., training organized by INSERM).

Team-by-team analysis

Team 1: Perinatal Epidemiology, Obstetrics and Pediatrics

We thank the committee members for its comprehensive and constructive comments on our research team. We would like to use this occasion to provide our comments on several of the points raised in the report.

- Recommendations: The management and maintenance of the large number of databases currently in the portfolio of the team 1 is both time and resource consuming. It would therefore be desirable to adopt the "COUNT" approach (i.e. Collect Once Use Numerous Times) when it comes to new data collection.

Our team is strongly involved in the implementation and coordination of large studies, which allows for investigating multiple questions in the field of perinatal, maternal and child health. Several of these studies have been set up to allow complementary and multidisciplinary projects on sub-populations to respond in more depth to questions that are difficult to deal with in the cohort as a whole. Moreover, data assembled for these studies will be accessible to all research groups, public or private, French or foreign. As underlined by the visiting committee of the AERES, this process is time and resource consuming, in particular because it is necessary to organize the following:

- the inclusion and follow up of a large number of children and women
- the collection, validation and correction of data
- the implementation of associated projects collecting additional information and, in particular, biological, clinical, and imaging data
- data access for research teams for analyses
- links with external data sources

The strong interactions within the team favor the continued use of the data from these studies by researchers working on different themes, as shown by the large number of publications from the National Perinatal Surveys as well the EPIPAGE 1 study (more than 50 studies). Our experiences within the team are invaluable for managing the new large platforms and projects proposed in our research project as well as for promoting wide diffusion and use of these data (in particular the RE-CO-NAI Platform).

- Recommendations: Theme 5 of team 1 should become a more integral part of the whole team 1 by investigating research questions affiliated to other cohorts studied in themes 1-4.

The team has contributed to the emergence of a new theme, that is, clinical epidemiology of routine practice in pediatrics, not covered elsewhere in France. Professor Martin Chalumeau is responsible for research on this theme, which aims to evaluate medical practices and their utility in routine pediatric practice, the applicability of clinical practice guidelines, and the production of diagnostic tools and strategies and new validated guidelines for optimizing routine care. This theme is consistent with other themes investigated by our team -- theme 1 (optimizing care in the general population) and theme 2 (suboptimal care) -- as well as research on non-optimal care in team 5 (P Ravaud). This is an important emerging theme developed in an environment recognized for its strengths in pediatrics (PRES Sorbone Paris Cité) including two of the three pediatric hospitals in Paris (Necker and Robert-Debré).

- Recommendations: More efforts could be made to study influences of inequalities among minorities, socially disadvantaged populations and of migrants, and to collaborate with groups with expertise in such issues.

There is concern that socioeconomic disparities in perinatal health outcomes in France have increased. The team's projects pay particular attention to social inequalities in relation to pregnancy outcome, screening for congenital anomalies, care of children with diseases or disabilities, maternal morbidity and access to care. These projects will be conducted with studies focused on the general population of pregnant women (National Perinatal Surveys, EURO-PERISTAT) as well as specific subpopulations (EPICARD, congenital anomalies, EPIPAGE, very preterm infants). The team is a founding member of the ROAM (Reproductive Outcomes and Migration) Collaboration,

an international network focused on promoting research into migrant reproductive health in high-income countries.

The French concept of "précarité" includes various aspects of economic and social deprivation, insecurity (e.g., temporary jobs) and vulnerability, which are strongly associated, among other things, with insufficient prenatal care. Given the extent of this vulnerability in Ile de France, the PreCARE project was developed to examine the best methods of improving access to and quality of care. This cohort, which includes 10,000 pregnant women from underprivileged areas in the north of Paris, coordinated by Dr Elie Azria (Team 1) and Pr Philippe Ravaud (Team 5), was set up to study the impact of maternal insecurity and deprivation on maternal and perinatal health. This study is an example of a collaborative study measuring consequences of inequalities among socially disadvantaged populations.

To continue work in this area, Dr Azria recently obtained a grant from the PRES for a project to analyze how the different dimensions of poverty and social vulnerability influence maternal and perinatal health (Précarité et trajectoires prénatales en Ile-de-France/Social Vulnerability and Care Trajectories in Ile-de-France). This project combines epidemiological and socio-anthropological methods.

Furthermore, the team was recently mandated by the Regional Health Agency in Ile-de-France to develop a study on the causes of high fetal and infant mortality in Seine-Saint-Denis, a socially disadvantaged district in the Paris region. This study, RéMIP, which began in January of 2012, focuses on the interaction between social disadvantage and perinatal care during pregnancy, delivery and the postpartum period to identify preventable factors associated with fetal and neonatal deaths.

- Recommendations: The team is multidisciplinary, but the disciplines represented are largely limited to different clinical specialties, epidemiologists and statisticians. The joint projects with microbiologists, genetics or other laboratory ('basic') scientists remain relatively small-scale and few in number. This is an area that could be developed over the next 5 years, particularly with respect to the potential for collection of samples / biobanks.

Although joint projects with teams from other disciplines are relatively small-scale and few in number, this process is ongoing and particularly new in our team. Collaborations have been established recently with teams working in the field of cell biology and genetics (two teams of UMRS 1016, the INSERM Unit U767 [physiology and human placental endocrinology], the EA4065 [the intestinal ecosystem, probiotics, antibiotics], EA1833 [oxidative stress, inflammatory response and cell proliferation]). There are frequent collaborations with the Necker-Cochin CIC on several current and future projects, which allows for collecting biological samples (placenta, blood etc.) for our studies. These collaborations will be reinforced by the recent creation of the Hospital University Department (DHU) grouping the 7 multidisciplinary research units working on perinatal health in the PRES.

Large cohorts that have been recently launched in our team represent an opportunity for collecting biological samples (EPIPAGE, EPICARD etc.), including as part of follow up. The organization of these studies as platforms is an important objective of our team for the future and an ongoing process that will facilitate multidisciplinary approaches and collaborations.

We are also involved in a new ambitious project called Better Intra-Uterine Growth (BIG) to investigate the causes and consequences of intra-uterine growth retardation. The project involves teams from basic sciences and epidemiology. Coordinated by Pr. Olivier Baud, the project is funded by the PREMuP foundation and will begin in the spring.

- Recommendations: The team could consider developing new partnerships with health economists or social scientists over the next 5 years. For example, some of the health services research would be strengthened by a health economics element, whilst there would be potential in the future to carry out research with the school-aged children with congenital heart abnormalities on quality of life.

The team has developed new national and international partnership with research teams working in various fields, including social scientists. Jennifer Zeitlin developed ties with the Department of

Health Evidence and Policy at the Mount Sinai Medical School in New York as part of a Marie Curie Fellowship International Outgoing Fellowship in 2010-2011. She current holds the position of Adjunct Associate Professor in the department. We also have developed collaborations with geographers in France to work on projects investigating access to health care and socio-spatial inequalities in perinatal health; two projects with geographers from other research groups are currently under way. Several of our projects, including the new TRAJECTOIRES project described above, the EPIMOMS project and the EPICE project, have integrated qualitative components requiring collaboration with sociologists and anthropologists. We recently recruited a midwife with a PhD in sociology to reinforce the team's capacity in this area.

Team 2: Biostatistics and Clinical Epidemiology

In the light of the AERES concluding recommendations, we wish to clarify the following points.

- Recommendations: To take full advantage of the opportunities of the collaborations within the research centre, it would seem appropriate to reinforce the critical mass of biostatisticians in this team and therefore to train young researchers able to apply for permanent positions. An alternative that should be discussed with the other teams would be to help to develop the statistical skills within teams that are in demand (mainly team 1 and 3). In this last scenario Team 2 could serve as a reference for statistics (training, expertise, validation of methods ...) for the centre.

We share the assessor's view that there is an unmet need to expand our staff of biostatisticians, and several measures are under way in this respect.

- We have applied for a permanent position at MCU-PH for one of our PhD students who will defend his dissertation in biostatistics by the end of this year.
- Two new university-teaching research assistants (AHU) will join our team in November 2013. One assistant has a background in biostatistics and will undertake a PhD in biostatistics in our team. The other assistant has a background in epidemiology, and she has been chosen to develop a fruitful collaboration with the epidemiological teams of the center. We hope that these research assistants will be able to apply for permanent positions in the future.
- Furthermore, our aim is to recruit an MCF for one of our biostatistical PhD researchers. We hope that university officials will help us in this aim, reinforced by our position in the center.
- We have developed in our university (Paris Diderot University), within the PRES, a full masters degree in public health, which is mostly devoted to clinical epidemiology and biostatistics with a second-year specialty dedicated to biostatistics for clinical epidemiology. This is a promising opportunity to create a flow of young researchers in that field in the next years.

Within the center, we have already developed two “statistical groups”: one directed towards researchers and the other to technicians from the center, with two main objectives:

- The aim of the first group is to help all the researchers from the center develop the statistical skills within their own team and axis of research. Indeed, the center offers the opportunity to formally organize what we have already done for many years, notably helping researchers develop their own skills (like one of our previous PhD students, now in team 4). This group should become an efficient communication channel between our team and other researchers on biostatistical issues, with whom several research projects are conducted, notably on Bayes approaches for clinical trials (with team 4) or on causal inference for cohort data (with teams 1 and 3).
- The second group aims at serving as a reference for training, expertise and validation of biostatistical methods applied in the center. Direct and practical interactions within this group will be developed to share statistical issues and computing codes, by using the website of our center.
- Both statistical groups are scheduled to meet once a month to share seminars on specific statistical topics in light of recommendations for scientific animation within the center.

- Recommendations: Exchanges and international collaborations with biostatistician should be pursued. Methodological developments could be submitted more frequently to highest level biostatistical journals.

With regard to exchanges and international collaborations with biostatisticians, ongoing and new ones are being developed.

- First, we aim at reinforcing prolonged collaborations that began with post-docs. This was exemplified by our collaboration with the MRC on multiple imputation (MI) methods, with two papers currently in preparation and a new participation of our team with a network of MI researchers in the UK, two years after this post-doc. This collaboration is likely to be

similar with Berkeley University, where one of our researchers is doing a post-doc this year. We think that the theme of causal inference will become more ambitious in the next few years, owing to interactions of researchers that benefit from innovations in other fields.

- Moreover, other collaborations will develop out of short visits to our team from foreign researchers. This was exemplified by our collaborative work on Bayesian adaptive randomization with the Dept. of Mathematical Statistics of George Washington University, which is nearly finished and will be submitted. A new collaboration, devoted to Bayes approaches for screening trials, was developed with the Dept. of Biostatistics of MD Anderson Cancer Center (Univ. of Texas, Houston) early this year, which we hope will be fruitful as well.

We recognize that we have possibly censored ourselves and that some of our papers might have not been sent to the highest-level biostatistics journals. According to these recommendations, we will try to be more ambitious in our upcoming submissions.

- Recommendations: On the other hand, clinicians of the team also have an excellent level of publications in clinical research. Most of these projects take advantage of the methodological development of the team but they pursue their own goals. Maybe these clinical projects could appear per se among the team's projects of research and not only as application of the methodological development.

The last point concerns the clinical projects of our team that may appear *per se* in the project rather than as only applications of the methodological developments. We agree that clinical epidemiology should appear on its own as the second main axis of our research, besides biostatistical research devoted to clinical issues, and this is exemplified by our production, training and research. The biostatistical research axis benefits from extensive collaborations with the physicians involved within and outside of our team, while the clinical epidemiology axis benefits from our biostatistical research too. Such an interaction is thus fruitful for both sides, biostatisticians on one hand and clinicians on the other. Thus, this permanent collaboration between biostatisticians and clinicians in our team is one of our major strengths.

Team 3: Nutritional Epidemiology

- Assessment of the five year plan and strategy, paragraph 2: The team has access to an impressive platform of databases derived from existing or ongoing cross-sectional and cohort studies (either randomized trials or observational studies) including the Nutrinet-Santé Study, generally coupled with well-organized biobanks. Despite the know-how of the team, there are, however, some concerns about the achievement of initial recruitment objectives (300 000 "true" participants) for the Nutrinet study due its funding uncertainty.

To date, the NutriNet-Santé study (which has a planned follow-up of 10 years) has included 120,000 fully enrolled participants. Recruitment is continuous, ongoing and growing steadily. The continuation of the recruitment does not depend on major financing (which was more pertinent at the beginning of the study when the development of the Internet tool took place). The amount of funding received in the future will largely determine the number of subjects that could be included in the Biobank (i.e., biological specimen storage), which now includes 14,000 subjects and has additional funding to reach 20,000 subjects. Given our extensive fundraising experience, we are hopeful that sufficient funding will be available to further increase the Biobank sample and pursue specific programs based on biomarker data.

Even if a sample of 300,000 cannot be reached, the number of included participants will guarantee sufficient statistical power to test most of our scientific hypotheses. If necessary, the duration of follow-up could be extended, especially with regard to specific hypotheses for rare conditions. Furthermore, the recent authorization by the State Council (dated 28 February 2013) will allow us to collect the NIR (social security number) and to have access to the national health care system database (SNIIRAM). These developments favor the realization of the planned investigation of the links among nutrition, cognition, and quality of aging, which pertains to one of the objectives of the NutriNet-Santé study (launched in 2009).

There is absolutely no threat with regard to the continuation of the NutriNet-Sante study. In fact, the most substantial part of the total cost (covered exclusively by public funding) of having this e-cohort was associated with the development of the Internet tool and website, most of which took place during the conception phase, and part of it took place over the first two years of the study. Our available financial resources will allow us to keep the cohort going and the recruitment open for at least the next 4 years (given the substantially reduced cost associated with recruitment and follow-up exclusively via the Internet). Regarding the Biobank, the premises and equipment (funded by Région Ile-de-France, University of Paris 13, and by ARC) are entirely adequate for the storage (at -80°C) of biospecimen samples for up to 40,000 individuals. The presently available financial resources will allow us to have at least 20,000 participants in the Biobank. Overall, the continuation of the cohort is not under any financial or other foreseeable threat over the next contract period (and possibly even much longer).

- Assessment of the five year plan and strategy, paragraph 3: The team plans to develop new research topics some of them being ambitious and innovative, like the introduction of web-based tools in large scale cohorts for reducing the costs and improving data management processes, the development of new tools in innovative research fields (such as the sensory and cognitive determinants of dietary and eating behaviours) or new instruments for assessing physical activity. The committee was however concerned by the risk of scattering of the internal forces with novel topics relating nutrition to cognition, chronic inflammatory diseases or reproduction disorders that may be promising but there are subjects to some uncertainties about the adequacy of tools (cohort, study design, staff) in some instances (multiple sclerosis, reproduction…).

Our program outline might have indeed given the impression that human and research resources would be scattered over a number of areas, and that some of the research tools might not be fully adapted to the specific objectives. In turn, the topics pertaining to the link between nutrition and cognition and between nutrition and fertility have been perceived by the committee as being new research venues. However, we would like to point out that these topics have been part of our research agenda for a number of years.

a) Regarding the "nutrition-cognition" domain, we have led an ANR-funded project on that topic (e.g., COMPALIMAGE: Dietary behaviours and quality of ageing: Role of inflammatory status,

oxidative stress, insulin resistance and genetic factors, 2005-2009). The study of the nutrition–cognition relationships was also a salient element of the SU.VI.MAX 2 study, in which more than 5,000 subjects recruited throughout France (and initially included in 1994 in the SU.VI.MAX cohort) underwent (in 2007) comprehensive neurocognitive evaluation by a trained neuropsychologist. In addition, the protocol of the SU.FO.OM3 trial specifically included the role of dietary supplementation on cognitive performance. Next, a number of articles on this topic have been published in high-quality journals, as can been seen from the examples provided below. Also, we have an ongoing, long-term collaboration with several experts from ISPED Bordeaux (e.g., Pascale Barberger-Gateau and Hélène Amieva).

The nutrition–cognition research domain is coordinated by Emmanuelle Kesse (CR1, HDR).

Selected publications:

- *Gillette GS, Abellan VK, Andrieu S, Barberger GP, Berr C., Bonnefoy M, Dartigues JF, De Groot L, Ferry M, Galan P, Hercberg S, Jeandel C, Morris MC, Nourhashemi F, Payette H, Poulain JP, Portet F, Roussel AM, Ritz P, Rolland Y, Vellas B. IANA Task Force on nutrition and cognitive decline with aging.* ***J Nutr Health Aging****, 2007, 11 (2) ,132-152. IF = 2,32*
- *Kesse-Guyot E, Peneau S, Ferry M, Jeandel C, Hercberg S, Galan P. Thirteen-year prospective study between fish consumption, long-chain n-3 fatty acids intakes and cognitive function.* ***J Nutr Health Aging****, 2011 15(2):115-120. IF = 2,48*
- *Kesse-Guyot E, Amieva H, Castetbon K, Henegar A, Ferry M, Jeandel C, Hercberg S, Galan P and the SU.VI.MAX 2 Research Group. Adherence to nutritional recommendations and subsequent cognitive performance: findings from the prospective SU.VI.MAX 2 study.* ***Am J Clin Nutr****, 2011 93(1):200-210. IF = 6,60*
- *Péneau S, Galan P, Jeandel C, Ferry M, Andreeva V, Hercberg S, Kesse-Guyot E, and the SU.VI.MAX 2 Research Group. Fruit and vegetable intake and cognitive function in the SU.VI.MAX 2 prospective study.* ***Am J Clin Nutr****, 2011 94(5):1295-1303. IF = 6,60*
- *Andreeva VA, Kesse-Guyot E, Barberger-Gateau P, Fezeu L, Hercberg S, Galan P. Cognitive function following supplementation with B-vitamins and long-chain omega-3 fatty acids: ancillary findings from the SU.FOL.OM3 randomized trial.* ***Am J Clin Nutr****, 2011. 94(1):278-286. IF = 6,60*
- *Kesse-Guyot E, Fezeu L, Jeandel C, Ferry M, Andreeva V, Amieva H, Hercberg S, Galan P. French adults' cognitive performance after daily supplementation with antioxidant vitamins and minerals at nutritional doses: a post hoc analysis of the Supplementation in Vitamins and Mineral Antioxidants (SU.VI.MAX) trial.* ***Am J Clin Nutr****, 2011. 94(3):892-899. IF =6,60.*
- *Kesse-Guyot E, Fezeu L, Andreeva VA, Touvier M, Scalbert A, Hercberg S, Galan P. Total and specific polyphenol intakes in midlife are associated with cognitive function measured 13 years later.* ***J Nutr,*** *2012 142(1):76-83. IF = 3,65*
- *Dangour AD, Andreeva VA, Sydenham E, Uauy R. Omega-3 fatty acids and cognitive health in older people.* ***Br J Nutr****, 2012; 107: S152–S158. IF=3,07*
- *Kesse-Guyot E, Charreire H, Andreeva VA, Touvier M, Hercberg S, Galan P, Oppert JM. Cross-sectional and longitudinal associations of different sedentary behaviors with cognitive performance in older adults.* ***PLoS One,*** *2012;7(10):e47831. IF = 4,09*
- *Kesse-Guyot E, Andreeva VA, Jeandel C, Ferry M, Touvier M, Hercberg S, Galan P. Alcohol consumption in midlife and cognitive performance assessed 13 years later in the SU.VI.MAX 2 cohort.* ***PLoS One,*** *2012;7(12):e52311. doi:10.1371/journal.pone.0052311. IF = 4,09*
- *Kesse-Guyot E, Andreeva VA, Lassale C, Ferry M, Jeandel C, Hercberg S, Galan P. Mediterranean diet and cognitive function: a French study.* ***Am J Clin Nutr****, 2013; 97(2):369-376. IF = 6,74*

In terms of the adequacy of the tools for study of the association between nutrition and cognition, we would like to draw attention to the SU.VI.MAX3 project, a prospective study involving "classic" evaluation methods such as neuropsychologist-administered cognitive test batteries. The subjects have been followed since 1994 and underwent a virtually identical neuropsychological assessment in 2007-2008. Thus, we will have the oppportunity to estimate cognitive decline over time.

The development of new, Internet-based methods for evaluating cognitive function is in progress in collaboration with Helene Amieva (ISPED, Bordeaux). The methods will include comparative testing or validation of the Internet tool against conventional methods before administration to the entire NutriNet-Santé cohort on a recurrent basis.

b) Regarding the "nutrition-fertility" domain, we initiated these investigations 3 years ago (in 2010) under the leadership of Dr. Rachel Levy (PU-PH). Over the last 3 years, we have been involved in the following 3 PHRC-funded projects:

- ***ALIFERT:*** *Impact of nutritional behaviours on couple infertility: multicenter case-control study. PHRC National 2010. Coordinator: UREN, project leader: Rachel Levy.*
- ***METASPERME****: Relations between sperm parameters and metabolic syndrome among male partners of infertile couples. PHRC National 2010. Coordinator: UREN, project leader: Rachel Levy*
- ***BARIASPERM****E: Impact of bariatric surgery on sperm quality among obese men (2011). Coordinator: UREN, project leaders: Sébastien Czernichow and Rachel Levy.*

These projects involve case–control studies and do not pertain to the NutriNet-Santé cohort.

The team has published several collaborative, comprehensive reviews on the topic, thus justifying interest in future research:

- *Sermondade N, Faure C, Fezeu L, Bonde JP, Shayeb G, Jensen TK, Van Wely M, Cao J, Martini AC, Eskandar M, Chavarro J, Koloszar S, Twigt J, Ramlau-Hansen CH, Borges Jr E, Lotti F, Steegers-Theunissen RPM, Zorn B, Polotsky AJ, La Vignera S, Eskenazi B, Tremellen K, Magnusdottir EV, Fejes I, Hercberg S, Lévy R, Czernichow. Body Mass Index in relation to sperm count: an updated systematic review and collaborative meta-analysis.* ***Human Reproduction Update*** *2012. doi: 10.1093/humupd/dms050.*
- *Sermondade N, Faure C, Fezeu L, Lévy R, Czernichow S, Obesity-Fertility Collaborative Group. Obesity and increased risk for oligozoospermia and azoospermia..* ***Arch Intern Med****, 2012; 172(5):440-2. IF = 10,64*

c) Regarding the "inflammatory diseases" domain, it is indeed an emerging topic of interest for our team. Its conception was related to the arrival of Dr. Chantal Julia (AHU), who is a candidate for a MCU-PH associate professorship position. The chronic inflammatory disease domain includes numerous and diverse pathologies. As a novel research area for our team, we decided to approach it by first working on a somewhat frequent pathology such as rheumatoid arthritis. This choice allowed for close collaborations with other teams in the Center. Future development of research protocols for other chronic inflammatory diseases will involve the same principles: i.e., investigation of relatively frequent pathologies with sufficient representation in our cohorts (e.g., NutriNet-Santé study) and providing the possibility to develop close collaborations with other teams with expertise in the domains of interest.

- Assessment of the five year plan and strategy, paragraph 4: Some scientific objectives (for example, the relationships of polyphenols, vitamin D, or weight change, with cancer or cardiovascular and metabolic diseases) appear more traditional and in strong competition with other groups at the national and international levels. In many cancer-related sub-projects, considering cancer as an overall entity is conceptually questionable in view of the large differences between site-specific cancers both in risk factors and in cancer biology. Cancer-site specific approach is mandatory but implies a risk of long-term responses (to be expand beyond the next contract).

We indeed welcome national or international competition regarding the role of nutrient intakes (polyphenols, vitamin D, etc.) in health outcomes. We have the research tools and expertise needed for such research endeavors. For instance, to our knowledge, we have at our disposal the most accurate polyphenol database, which includes 502 individual polyphenols from 452 different foods. The database has already been merged with the SU.VI.MAX database and is in the process of being merged with the NutriNet-Santé database. We have already started publishing on the topic in highly-respected journals (including publications on the links between polyphenols and cancer, polyphenol intake and cognition, polyphenols and weight change, etc.).

The launching of the NutriNet-Santé study online was one of the reasons to ensure the availability of a very large prospective cohort with a sufficient number of cases of interest. In addition, the issue of statistical power will not be of concern for the analyses. Finally, the recent authorization by the State Council (dated 28 February 2013) will allow us to collect the NIR (social security number) and to have access to the national health care system database (SNIIRAM). These developments, in turn, will allow us to have access to accurate data regarding cancer sites, treatment, and recurrence.

Regarding the relationship between nutrition and "traditional" pathologies, we would like to underline the fact that many associations still need to be confirmed and/or clarified. Moreover, the mechanistic pathways by which nutritional factors intervene in carcinogenesis are still poorly understood. We are confident that our team has the skills and tools to be internationally competitive in this domain and to further scientific knowledge. We have already published a number of articles in the nutrition-cancer field in highly-respected journals (JAMA Intern Med (formerly Arch Intern Med), Am J Clin Nutr, Am J Epidemiol, etc.).

Further, compared to large traditional cohorts focused on the nutrition-cancer link, the NutriNet-Santé study presents several advantages, such as:

- High-quality, comprehensive assessment of nutritional intake via repeated 24-h dietary records, supplemented with food frequency questionnaires and biomarker data. In addition, we are in a position to add ad hoc questionnaires depending on the exposures of interest. We also have expertise in variance reduction methods used in the assessment of usual nutrient intake, etc. In turn, several existing "traditional" cohorts rely on a single 24-h dietary recall, which is insufficient to accurately characterize nutritional exposures.
- Biobank with biological data from 20,000 participants, allowing us to perform analyses on nutritional biomarkers and to include mechanistic epidemiology approaches in our research. In addition, participants can be invited to undergo a biological examination "on demand," depending on ancillary protocols.
- Our team is a pioneer in the development/adaptation of high-quality food composition tables. To our knowledge, we have at our disposal the most accurate polyphenol database (Phenol-Explorer), which includes 502 individual polyphenols from 452 different foods. It has already been merged with the SU.VI.MAX database and is in the process of being merged with the NutriNet-Santé database. We have already started publishing on the topic in highly respected journals. We are also the first team internationally to publish findings derived from the Phenol Explorer database.
- Regarding case ascertainment, the validation of each major health event by an expert committee ensures the possibility to study accurately-defined pathologies (unlike data available from registries). For breast cancer, for instance, we record the cancer location as well as the histological type, the ER/PR receptor status, the parameters regarding invasiveness of the tumor, the number of nodes, etc.
  As presented in our report (and also during the oral evaluation), site-specific analyses will be performed to study the relationship between nutrition and cancer. In fact, we have already conducted such analyses (mostly for breast, prostate, skin, and colorectal cancer). This was also one of the reasons for launching the NutriNet-Santé study. This cohort allows for studying a large number of subjects for a long period of time. Thus, cancer incidence is expected to be relatively high (as calculated and explained in the study protocol). Furthermore, the recent authorization by the State Council (dated 28 February 2013) will allow us to collect the NIR (social security number) and to have access to the national health care system database (SNIIRAM). These developments are important because they will allow us to overcome limitations regarding, for example, loss to follow-up. The size of our cohort is entirely suitable in terms of statistical power for site-specific analyses, both for major cancer sites and for rarer tumor locations.
  In turn, several existing cohorts focus only on one major pathology (e.g., cancer or cardiovascular disease but not both), whereas we systematically record and validate all major pathologies in the same cohort. This allows us to have a good grasp of common and/or competitive risks as well as co-morbidities.
- Many well-established cohorts are now composed of relatively older participants, whereas subjects of the NutriNet-Santé study are younger (ages 18+). This will allow us to study the relationship between nutrition and the onset of chronic diseases starting earlier in life.
- Our Internet tool allows us to easily collect information on any nutritional exposures that might become of interest in the near future (i.e., entails great adaptability).

- Recommendations: The participation in international training programs could be a target in the future in order to improve international collaborations and the exchange of researchers.

We share the assessor's view about the need to improve this point. We have just started discussions to develop an international training program in nutritional epidemiology with Imperial College, London. Moreover, in 2014 our team plans to be in charge of a module dedicated to e-epidemiology within the master's program in advanced epidemiology established by Philippe Ravaud and Pierre Yves Ancel. The degree will be taught entirely in English by professors from the Universities of Paris Descartes and other universities as well as by international experts in epidemiology and will attract international students. Classes on nutritional epidemiology will be also given by members of the team in this master's program.

- Recommendations: The team should be proactive for cross-cutting research exchanges on nutrition within the Centre. There seems to exist a short-term opportunity to study nutrition during gestation (Team 1).

We fully agree with this recommendation. As we indicated in our oral presentation, we have planned to develop collaborations with Team 1 in the field of nutrition and pregnancy. Several meetings involving teams 1 and 3 researchers have been organized thus far to identify specific scientific questions of interest to both teams. Some points of interest include the consumption of light foods, supplement use, evolution of dietary habits during pregnancy, role of specific nutrients, etc. The number of pregnant women in the NutriNet cohort has been assessed (about 7,000 new pregnancies have been reported since the study was launched). This will allow us to develop ancillary protocols in this field.

One topic that we will address together with team 1 and which is of high public heath priority is the assessment of dietary supplement use during pregnancy. Indeed, some key nutrients (such as folic acid) should be consumed before and just at the beginning of pregnancy to prevent neural tube defects. In contrast, several arguments encourage caution regarding supplement use as self-medication during pregnancy for some nutrients. They pertain to the potential toxicity associated with overdose of some nutrients or bioactive compounds (such as retinol, vitamin E, phytoestrogens, etc.) and the potential deleterious effects of some herbal supplements, alone or when combined with medication use. Detailed data on dietary supplement use (and its determinants) during pregnancy is scarce internationally and no data have been published for the situation in France; thus, our collaboration with team 1 will bring new information regarding this important topic.

Team 2 will be join the discussions to upgrade statistical methods to study the relationship between nutrition (role of foods, nutrients, dietary behavior, physical activity) and gestation.

- Recommendations: The team should increase its expertise in novel statistical methods as well as in physical activity and sport sciences as it is an important emerging topic in the group (Team 2). As nutrition is more and more integrated in the lifestyle concept, the physical activity part should grow in the next years and probably will need some reinforcement.

We fully agree that the physical activity component should be viewed in a comprehensive manner in terms of lifestyle and health. This is in line with our interest in developing this specific research topic through the extension of our studies on methods to assess physical activity (and sedentary behavior) and our studies on the geographical effects on the relationship between physical activity and health. Our collaboration with team 2 (Sylvie Chevret) would provide an opportunity to include advanced statistical modeling in this domain and upgrade our methods in terms of analysis plans. Specifically, we are working with team 2 to upgrade our statistical skills regarding innovative missing data management, management and treatment of statistical data from metabolomics projects, inclusion of competitive risk parameters in our models, and improvement of our statistical methods for meta-analyses.

The physical activity component of our research agenda will be further strengthened by Didier Chapelot (MCF assistant Professor, section CNU 74, STAPS, Technical Sciences in Physical Activity and Sports) who will join our team in 2014.

- Recommendations: The team should more clearly define research priorities in order to focus on innovative fields with high probability of outstanding publications, and develop an appropriate strategy for setting up projects with the other teams of the Centre.

We fully agree that it is important to define the research priorities. In terms of both the predictors of dietary behaviors and the link between diet/nutrition and health/disease, we will strive to advance knowledge and address major public health challenges. We will also develop and use novel research tools (e.g., a large e-cohort with detailed data on dietary exposures, physical activity, and health status). In terms of the various specific study protocols (e.g., cancer, CVD, metabolic conditions, cognition, etc.), our research tools will allow us to approach these topics in an innovative manner (compared to existing cohorts on the international level, which use conventional approaches). This strategy, coupled with the advanced statistical methodology to be used as a result of our collaborations within the Center, will certainly help us augment the quantity and quality of our publications.

- Recommendations: The committee recommends to pursue the discussions and coaching for a future leader of the team.

As indicated under Factual Errors, Serge Hercberg (PU-PH) will lead the team until the end of his term (2014-2018). Serge Hercberg will retire as University Professor in 2019. Neither Pr. Hercberg nor the members of team 3 plan on any leadership changes during the upcoming contract period. Given that Pr. Hercberg will retire as director at the end of the next term (2018), internal, preliminary discussions have indeed begun and will continue during the next years. Two potential leaders have been identified. They have been fully invested in the development of the research agenda for the upcoming contract. They have also contributed to the current responses to the comments in the AERES report. They will be progressively more involved in the life and in different aspects of the management of the Unit. They will be fully trained by the current Director. A collegial decision will be made in 2016 to choose the future leader who will be named Assistant Director and will be ready to develop the future project of the team. That person will be assisted by the other researchers and leaders of the different research axes.

Team 4: Clinical Epidemiology applied to osteo-articular diseases

- Weaknesses and threats: Team based mostly on clinicians with no permanent epidemiological researcher"

- Recommendations: Increase internal resources in epidemiology to supervise PhD students in clinical epidemiology

Two members of the team have a formal training in epidemiology/biostatistics. However, most members of the team have training through long-term collaborations with epidemiologists and biostatisticians (mainly teams 2 and 5), which can be considered a long-term learning program. One member of the team (MD) is the author of a book entitled *Measures in Rheumatology,* that has been widely distributed. These skills lead several members of the team to play a very active and important role in the OMERACT (Outcome Measures in Rheumatology) initiative. Over the last 20 years, OMERACT has played a critical role in the development and validation of clinical and radiographic outcome measures in rheumatology and is considered a model for many specialties. Members of the team have been involved of many national and international cohort studies dedicated to rheumatic diseases. In addition, a half-time experienced associate professor in epidemiology will be recruited for the next 2 years.

- Weaknesses and threats: Lack of implication in training in epidemiology/biostatistics.

- Recommendations: Clarify more precisely the strategy planned to improve training through research and the analysis of the usable skills and resources available and able to be deployed.

Concerning training through research, because the team was not officially recognized as research team during the last 5 years, it was impossible to be officially in charge of research doctoral students. However, 6 master's trainees were coached by members of the team during this period and 3 doctoral students were jointly supervised. The number of residents from foreign countries received illustrates the ability of the team members to train younger researchers.

The strategy of the team to improve our ability to train through research is constructed in 3 main steps. First, we will increase our collaborations with the other teams of the centre: reinforcement with teams 5 and 2 and new collaborations with team 1 (qualitative approaches) and 3 (e-cohorts). Therefore, these collaborations as well as a systematic formal training of younger members of the team and permanent epidemiological/biostatistics coaching from teams 5 and 2 will lead to progressively increasing our autonomy to develop our projects and our ability to train through research. Finally, we will recruit among the young collaborators with formal epidemiological training within the team or the centre a member that will become one of the leaders of the unit.

- Weaknesses and threats: Lack of specific prospective strategy in terms of scientific agenda and in terms of team building

- Recommendations: Need to develop the more specific research agenda focused on clinical epidemiology applied to rheumatic and musculoskeletal disorders, with need of epidemiological coaching

Our strategies in terms of scientific agenda, team building, and training through research are linked and progressive. As an emerging team, we are glad to benefit from the skills of the other teams of the centre, and especially teams 5 and 2. We receive intensive systematic epidemiological and biostatistical coaching for our individual research projects. We must recognize that we have more expertise to develop specific research projects than a 5-year research plan and strategy. However, progressively, with the help and coaching of the other teams, we will make progress in this way, and certainly the 5-year research program we would write today would be quite different and more specific that the one we wrote during summer 2012.

- Assessment of the five-year plan and strategy: Other original developments are being considered such as learning curves for low back pain patients that are promising. This sub-theme is part of theme 1 but the coherence of this is not strait forward; it could be envisaged to consider this topic in an individual theme

Concerning the learning curve project, it is one of our priorities and the theme of a doctoral thesis (CP). From our point of view, its position in theme 1 is quite logical because one of the key issues to define these learning curves is to determine the best outcome to define competency.

- Assessment of the five-year plan and strategy: Other sub-themes are original such as patient-reported outcomes, although no collaborations are planned with other French teams working in the field

- Recommendations: Increase knowledge and collaborations with other French teams working in the field.

About the patient-reported outcome theme, to our knowledge, no INSERM team is devoted to this topic. However, we have been working in this field since the early 1990s and have collaborated with several French statisticians or methodologists over this period (Jacques Fermanian, Bruno Falissard occasionally, Philippe Ravaud, and Sylvie Chevret) and many methodologists and epidemiologists all over the world working specifically on patient-reported outcomes in the field of rheumatic diseases (Peter Tugwell, Ottawa University; Martin Boers, VU Medical Center, Amsterdam; Marc Hochberg, University of Maryland School of Medicine; David Felson, Boston University School of Medicine). These collaborations within the centre are ongoing and we are planning to work again with Bruno Falissard (INSERM unit U669) on the methodological issues raised by qualitative approaches.

Team 5: Method of therapeutic evaluation: Chronic diseases

- Weaknesses and threats: The objectives of the research program tend to be a bit unspecific and the methodology for the program became sometimes unclear during oral presentation and question and answer session.
- Recommendations: To be more specific when defining the objectives of the proposed research program.

We completely agree that in the project and during the presentation, one of the projects related to the complex system approach could appear unspecific and not detailed enough.

In fact, our theme on complexity focuses on several issues: some of them concerned matured projects that will be developed soon and some projects using new emerging concepts need more maturation and were consequently less detailed in our document. It is actually difficult to be very specific and detailed for a new and highly innovative research theme that we plan to develop during our 5-year research program. Moreover, it is also more difficult to be responsive and subtle in briefly explaining innovative concepts together with detailed methodology when answering questions in a foreign language.

Since the experts' visit, however, some of our projects about complex system have evolved and 2 grants have been submitted on this topic. A short summary of these projects is provided below and the full executive summary is reported in the appendix.

- Grant proposal ANSM: Project "IBR² Inversion of the Benefit Risk Ratio"
  The inverse-benefit law, a new paradigm, states that the benefit-risk ratio in patients taking new drugs tends to vary inversely with how extensively the drug is marketed, not only because of lack of generalizability of trials, but also because of marketing strategies by pharmaceutical companies. Their goal would thus be to enlarge the treated population. This expansion to a less affected population with less severe symptoms could result in decreased benefit. The overall aim of this project is to better understand the evolution of the benefit-to-risk ratio during the post-marketing period and to reveal an indicator to alert the regulatory authorities of the need to reassess the benefit-risk balance for a new marketed drug before inversion of its benefit-risk ratio.
- Grant proposal for the ANSM "DEFI² detection of adverse events in a complex system"
  Post-marketing drug surveillance using huge medical-administrative databases presents two major challenges. First surveillance should allow both to identify already hypothesized associations and to detect unsuspected associations. Second, the methods used should be able to be used with the huge databases. Our project aims to assess the potential value of recent statistical risk methods derived from the statistical learning theory for post-marketing drug surveillance using the SNIIR-AM database. The methodology will use simulated adverse events introduced in the SNIIR-AM database so that sensitivity will be estimated. Methods will then be used to analyze the real SNIIR-AM database without making prior hypotheses.

- Recommendations: To develop cross-cutting research project with other teams (1 and 3 for example).

Since the experts' visit, several cross-cutting projects have been initiated or moved forward.

For instance, we have 5 joint projects with team 1:

- The PreCARE cohort of 10,000 pregnant women that aims to study the impact of maternal insecurity and deprivation on maternal and perinatal health
- Prioritization of research into caesarean section
- New methods for the evaluation of clinical practices in the field of post-partum hemorrhage
- Quality of reporting of studies evaluating diagnostic delay in pediatric diseases
- Meta-epidemiologic study assessing the impact of blinding on treatment effect estimates in RCTs assessing treatment of labor induction.

We are also developing an important new project with teams 3 and 4 of a large e-cohort dedicated to chronic diseases and multimorbid patients.

Appendix

Grant proposal for the ANSM "DEFI² detection of adverse events in a complex system"

At time of marketing authorization of a drug, only limited data are available to determine its safety profile. Post-marketing surveillance is thus undertaken to gather information on this safety profile, mainly based on spontaneous reporting of adverse events.

The use of observational databases could significantly increase the performance of post-marketing surveillance of drug safety, and several internal initiative have been launched to promote the use of observational huge medical-administrative databases. Given the lack of shared database structure and accessibility between countries, country-specific approaches remain necessary.

Post-marketing drug surveillance with huge medical-administrative databases presents two major challenges. First surveillance should allow for both identifying already hypothesized associations and to detect unsuspected associations. Second, the methods used should be able to be used with the huge databases (thousands of variables for millions of patients), when statistical methods prove inefficient in such situation.

Our project aims to assess the potential value of recent statistical risk methods derived from the statistical learning theory for post-marketing drug surveillance with administrative databases, more specifically the SNIIR-AM database.

More precisely, the goal is to create from the SNIIR-AM database a sample of several tens of millions of individuals to assess the ability of the new methods to detect artificially induced adverse effects. The adverse effects will be introduced in the data according to scenarios representing a wide range of plausible situations. Then a large data or testing approach for data analysis will be used. First, innovative statistical methods from statistical learning theory and data mining will be used to generate hypotheses. Then more classical statistical methods will be used to test these hypotheses. The methodology will use simulated data so that sensitivity will be estimated (i.e., the ability of a method to detect the associations that have been introduced in the data).

The first expected result is the estimation of the performance of the detection strategy we propose to detect weak signals in the huge SNIIR-AM database.

Methods will then be used to analyze the real SNIIR-AM database without making prior hypotheses. If the method detects associations (signals), then they will be discussed with an expert working group and "classical" statistical methods will be used to confirm the resulting hypotheses. Two types of applications can be considered: a retrospective analysis of SNIIR-AM database on existing products and a prospective analysis following the introduction of a new drug. This could be used in the future by the ANSM for new drugs.

Finally, anonymous simulated data will be made publicly available for other researchers to promote development and validation of other new methods.

Grant proposal ANSM: Project "IBR² Inversion of the Benefit Risk Ratio"

The assessment of the benefit-risk ratio of a drug is a major responsibility of regulatory authorities. Before a marketing authorization, the benefit-risk ratio is appraised with available estimates of efficacy and safety, mainly obtained in phase III randomized controlled trials.

However, a constant reevaluation of the benefit-risk ratio is necessary after drug approval because it may change with time. There are several reasons explaining the change in how the benefit-risk ratio is appraised. First, clinical trials are mostly powered to demonstrate the efficacy of a drug but rarely to assess its safety, and rare events are unlikely to be detected before approval because of too-small sample size or too-short follow-up. Second, patients with a potentially higher risk of toxicity are often underrepresented (or even excluded) from clinical trials, such as the elderly population or multi-morbid patients. However, once on the market, the drug will be prescribed to these patients, and thus safety concerns may increase. Finally, a new paradigm has been recently introduced, the inverse-benefit law. This heuristic law states that the benefit-risk ratio in patients taking new drugs tends to vary inversely with how extensively the drug is marketed, because of lack of generalizability of trials and because of marketing strategies by pharmaceutical companies. Their

goal would thus be to enlarge the treated population. This expansion to a less affected population with less severe symptoms could result in decreased benefit.

The overall aim of this project is to better understand the evolution of the benefit- to-risk ratio during the post-marketing period and to reveal an indicator to alert the regulatory authorities of the need to reassess the benefit-risk balance for a new marketed drug before inversion of its benefit-risk ratio.

The first step will be to quantify the impact of inverse-benefit law and underrepresentation of high-risk patients in trials on the benefit-risk ratio. This step will be performed using an extensive simulation study with a wide range of scenarios derived from a thorough review of the literature and analysis of medical-administrative databases and registries of clinical practice.

Then a "distance" will be developed to evaluate how far the treated population in the "real world" is from the population included in phase III trials. This distance will be constructed so that (i) it is associated with the variation of the benefit-risk ratio and (ii) it can be computed with data available in existing medical-administrative databases (here the SNIIR-AM database). As such it will be usable by health authorities as an objective tool for real-time monitoring of the potential evolution of the benefit-risk ratio of drugs.

A publicly available simulation tool will be derived from the two previous steps. It will allow research organizations or health authorities to apply our findings on their own data.

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Villetaneuse, le 22 avril 2013

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Observations générales sur le rapport AERES du Centre de Recherche Inserm en Epidémiologie et Biostatistique, concernant le bilan de l'équipe 3 : Unité de Recherche en Epidémiologie Nutritionnelle (UREN, Paris 13 / U557 Inserm / U1125 INRA /CNAM)

L'université tient tout d'abord à saluer la qualité du comité, des échanges lors de la visite et du rapport fourni et elle se félicite de sa tonalité générale très positive.

L'établissement se réjouit de voir confirmées quelques très grandes qualités et spécificités de cette équipe, en particulier le très haut niveau de sa production scientifique, de ses financements et de sa réputation au niveau national et international et le très grand potentiel des ses e-cohortes.

Nous prenons acte des quelques faiblesses pointées, notamment en ce qui concerne le danger de dispersion thématique, et des recommandations associées, notamment pour associer les études nutritionnelles avec celles d'autres équipes du centre de recherche et pour préparer le futur leadership de l'équipe.

L'université se félicite de participer pleinement à la construction de ce projet de grand centre de recherche en épidémiologie et biostatistique au sein du PRES Sorbonne Paris Cité et en association avec l'Inserm et l'INRA. Comme les autres, l'équipe de Paris 13 y trouvera une dynamique de collaboration scientifique et de mutualisation des ressources et des savoir faire et une visibilité nationale et internationale accrue.

Des réponses plus spécifiques de l'équipe, sur quelques points importants du rapport, sont données à la suite de ces observations générales.

Jean-Loup SALZMANN

TEAM 3 «NUTRITIONAL EPIDEMIOLOGY»

RESPONSES TO COMMENTS AND RECOMMENDATIONS

1. <u>Page 20, Assessment of the five year plan and strategy, Paragraph 2</u> ***"The team has access to an impressive platform of databases derived from existing or ongoing cross-sectional and cohort studies (either randomized trials or observational studies) including the Nutrinet-Santé Study, generally coupled with well-organized biobanks. Despite the know-how of the team, there are, however, some concerns about the achievement of initial recruitment objectives (300 000 "true" participants) for the Nutrinet study due its funding uncertainty."***

To date, the NutriNet-Santé study (which has a planned follow-up of 10 years) has included 120,000 fully enrolled participants. Recruitment is continuous, ongoing and growing steadily. The continuation of the recruitment is not dependent on major financing (which was more pertinent at the beginning of the study when the development of the Internet tool took place). The amount of funding received in the future will largely determine the number of subjects that could be included in the Biobank (ie, biological specimen storage), which now includes 14,000 subjects and has additional funding to reach 20,000 subjects. Given our extensive fundraising experience, we are hopeful that sufficient funding will be available in due course to further increase the Biobank sample in order to pursue specific programs based on biomarker data.
Even if a sample of 300,000 cannot be reached, the number of included participants will guarantee sufficient statistical power to test most of our scientific hypotheses. If necessary, the duration of follow-up could be extended, especially as regards specific hypotheses bearing on rare conditions. Furthermore, the recent authorization by the State Council (dated 28 February 2013) will allow us to collect the NIR (social security number) and to have access to the national health care system database (SNIIRAM). These developments favor the realization of the planned investigation of the links among nutrition, cognition, and quality of aging which pertains to one of the objectives of the NutriNet-Santé study (launched in 2009).
There is absolutely no threat as regards the continuation of the NutriNet-Sante study. In fact, the most substantial part of the total cost (covered exclusively by public funding) of having this e-cohort was associated with the development of the Internet tools and website, most of which took place during the conception phase and part of it took place over the first two years into the study. Our available financial resources will allow us to keep the cohort going and the recruitment open for at least the next 4 years (given the substantially reduced cost associated with recruitment and follow-up exclusively by Internet). Regarding the Biobank, the premises and equipment (funded by Région Ile-de-France, University of Paris 13, and by ARC) are entirely adequate for the storage (at -80°C) of biospecimen samples of up to 40000 individuals. The presently available financial resources will allow us to have at least 20000 participants in the Biobank. Overall, the continuation of the cohort is not under any financial or other foreseeable threat over the next contract period (and possibly even much longer).

2. <u>Page 20, Assessment of the five year plan and strategy, paragraph. 3:</u> ***"The team plans to develop new research topics some of them being ambitious and innovative, like the introduction of web-based tools in large scale cohorts for reducing the costs and improving data management processes, the development of new tools in innovative research fields (such as the sensory and cognitive determinants of dietary and eating behaviours) or new instruments for assessing physical activity. The committee was however concerned by the risk of scattering of the internal forces with novel topics relating nutrition to cognition, chronic inflammatory diseases or reproduction disorders that may be promising but there are subjects to some uncertainties about the adequacy of tools (cohort, study design, staff) in some instances (multiple sclerosis, reproduction…)."***

Our program outline might have indeed given the impression that human and research resources would be scattered over a number of areas, and that some of the research tools might not be fully adapted to the specific objectives. In turn, the topics pertaining to the link between nutrition and cognition and the link between nutrition and fertility have been perceived by the committee as being new research venues. We would like to point out, however, that these topics have been part of our research agenda for a number of years.

As regards the «nutrition - cognition» domain, we have led an ANR-funded project on that topic (eg, COMPALIMAGE: Dietary behaviours and quality of ageing: Role of inflammatory status, oxidative stress, insulin resistance and genetic factors (2005-2009). The study of the nutrition-cognition relationships was also a salient element of the SU.VI.MAX 2 study, where more than 5 000 subjects recruited throughout France (and initially included in 1994 in the SU.VI.MAX cohort) underwent (in 2007) a comprehensive neurocognitive evaluation by a trained neuropsychologist. In addition, the protocol of the SU.FO.OM3 trial included specifically the role of dietary supplementation on cognitive performance. Next, a number of articles on this topic have been published in high-quality journals, as can been seen from the examples provided below. Also, we have an ongoing, long-term collaboration with several experts from ISPED Bordeaux (for example, Pascale Barberger-Gateau and Hélène Amieva).
The nutrition-cognition research domain is coordinated by Emmanuelle Kesse (CR1, HDR).
Selected publications:

- *Gillette GS, Abellan VK, Andrieu S, Barberger GP, Berr C., Bonnefoy M, Dartigues JF, De Groot L, Ferry M, Galan P, Hercberg S, Jeandel C, Morris MC, Nourhashemi F, Payette H, Poulain JP, Portet F, Roussel AM, Ritz P, Rolland Y, Vellas B. IANA Task Force on nutrition and cognitive decline with aging.* ***J Nutr Health Aging****, 2007, 11 (2) ,132-152. IF = 2,32*
- *Kesse-Guyot E, Peneau S, Ferry M, Jeandel C, Hercberg S, Galan P. Thirteen-year prospective study between fish consumption, long-chain n-3 fatty acids intakes and cognitive function.* ***J Nutr Health Aging****, 2011 15(2):115-120. IF = 2,48*
- *Kesse-Guyot E, Amieva H, Castetbon K, Henegar A, Ferry M, Jeandel C, Hercberg S, Galan P and the SU.VI.MAX 2 Research Group. Adherence to nutritional recommendations and subsequent cognitive performance: findings from the prospective SU.VI.MAX 2 study.* ***Am J Clin Nutr****, 2011 93(1):200-210. IF = 6,60*
- *Péneau S, Galan P, Jeandel C, Ferry M, Andreeva V, Hercberg S, Kesse-Guyot E, and the SU.VI.MAX 2 Research Group. Fruit and vegetable intake and cognitive function in the SU.VI.MAX 2 prospective study.* ***Am J Clin Nutr****, 2011 94(5):1295-1303. IF = 6,60*
- *Andreeva VA, Kesse-Guyot E, Barberger-Gateau P, Fezeu L, Hercberg S, Galan P. Cognitive function following supplementation with B-vitamins and long-chain omega-3 fatty acids: ancillary findings from the SU.FOL.OM3 randomized trial.* ***Am J Clin Nutr****, 2011. 94(1):278-286. IF = 6,60*
- *Kesse-Guyot E, Fezeu L, Jeandel C, Ferry M, Andreeva V, Amieva H, Hercberg S, Galan P. French adults' cognitive performance after daily supplementation with antioxidant vitamins and minerals at nutritional doses: a post hoc analysis of the Supplementation in Vitamins and Mineral Antioxidants (SU.VI.MAX) trial.* ***Am J Clin Nutr****, 2011. 94(3):892-899. IF =6,60.*
- *Kesse-Guyot E, Fezeu L, Andreeva VA, Touvier M, Scalbert A, Hercberg S, Galan P. Total and specific polyphenol intakes in midlife are associated with cognitive function measured 13 years later.* ***J Nutr,*** *2012 142(1):76-83. IF = 3,65*
- *Dangour AD, Andreeva VA, Sydenham E, Uauy R. Omega-3 fatty acids and cognitive health in older people.* ***Br J Nutr****, 2012; 107: S152–S158. IF=3,07*
- *Kesse-Guyot E, Charreire H, Andreeva VA, Touvier M, Hercberg S, Galan P, Oppert JM. Cross-sectional and longitudinal associations of different sedentary behaviors with cognitive performance in older adults.* ***PLoS One,*** *2012;7(10):e47831. IF = 4,09*
- *Kesse-Guyot E, Andreeva VA, Jeandel C, Ferry M, Touvier M, Hercberg S, Galan P. Alcohol consumption in midlife and cognitive performance assessed 13 years later in the SU.VI.MAX 2 cohort.* ***PLoS One,*** *2012;7(12):e52311. doi:10.1371/journal.pone.0052311. IF = 4,09*
- *Kesse-Guyot E, Andreeva VA, Lassale C, Ferry M, Jeandel C, Hercberg S, Galan P. Mediterranean diet and cognitive function: a French study.* ***Am J Clin Nutr****, 2013; 97(2):369-376. IF = 6,74*

As regards the adequacy of the tools for the study of the association between nutrition and cognition, we would like to draw attention to the SU.VI.MAX3 project, which is a prospective study employing «classic» evaluation methods, such as neuropsychologist-administered cognitive test batteries. The subjects have been followed since 1994 and have undergone a virtually identical neuropsychological assessment in 2007-2008. Thus, we will have the oppportunity to estimate cognitive decline over time.

The development of new, Internet-based methods for evaluating cognitive function is in progress in collaboration with Helene Amieva (ISPED, Bordeaux). It will include comparative testing / validation of the Internet tool against conventional methods before being administered to the entire NutriNet-Santé cohort on a recurrent basis.

b) ***As regards the «nutrition - fertility» domain***, we initiated these investigations 3 years ago (ie, in 2010) under the leadership of Dr. Rachel Levy (PU-PH). Over the last 3 years, we have been involved in the following 3 PHRC-funded projects:

- ***ALIFERT:*** *Impact of nutritional behaviours on couple infertility: multicenter case-control study. PHRC National 2010. Coordinator: UREN, project leader: Rachel Levy.*
- ***METASPERME****: Relations between sperm parameters and metabolic syndrome among male partners of infertile couples. PHRC National 2010. Coordinator: UREN, project leader: Rachel Levy*
- ***BARIASPERME****: Impact of bariatric surgery on sperm quality among obese men (2011). Coordinator: UREN, project leaders: Sébastien Czernichow and Rachel Levy.*

These projects entail case-control studies and do not pertain to the NutriNet-Santé cohort.
The team has published several collaborative, comprehensive reviews on the topic, thus justifying interest in future research:

- *Sermondade N, Faure C, Fezeu L, Bonde JP, Shayeb G, Jensen TK, Van Wely M, Cao J, Martini AC, Eskandar M, Chavarro J, Koloszar S, Twigt J, Ramlau-Hansen CH, Borges Jr E, Lotti F, Steegers-Theunissen RPM, Zorn B, Polotsky AJ, La Vignera S, Eskenazi B, Tremellen K, Magnusdottir EV, Fejes I, Hercberg S, Lévy R, Czernichow. Body Mass Index in relation to sperm count: an updated systematic review and collaborative meta-analysis.* ***Human Reproduction Update*** *2012. doi: 10.1093/humupd/dms050.*
- *Sermondade N, Faure C, Fezeu L, Lévy R, Czernichow S, Obesity-Fertility Collaborative Group. Obesity and increased risk for oligozoospermia and azoospermia..* ***Arch Intern Med****, 2012; 172(5):440-2. IF = 10,64*

c) ***As regards the «inflammatory diseases» domain*** - it is indeed an emerging topic of interest for our team. Its conception was related to the arrival of Dr. Chantal Julia (AHU), who is a candidate for a MCU-PH associate professorship position. The chronic inflammatory disease domain includes numerous and diverse pathologies. As a novel research area for our team, it was decided to approach it by first working on a somewhat frequent pathology such as rheumatoid arthritis. This choice permitted close collaborations with other teams in the Center. Future development of research protocols for other chronic inflammatory diseases will be conducted using the same principles: i.e., investigation of relatively frequent pathologies with sufficient representation in our cohorts (eg, NutriNet-Santé study) and providing the possibility to develop close collaborations with other teams with expertise in the domains of interest.

3. Page 20, Assessment of the five year plan and strategy, paragraph. 4: ***"Some scientific objectives (for example, the relationships of polyphenols, vitamin D, or weight change, with cancer or cardiovascular and metabolic diseases) appear more traditional and in strong competition with other groups at the national and international levels. In many cancer-related sub-projects, considering cancer as an overall entity is conceptually questionable in view of the large differences between site-specific cancers both in risk factors and in cancer biology. Cancer-site specific approach is mandatory but implies a risk of long-term responses (to be expand beyond the next contract)."***

We indeed welcome national or international competition regarding the role of nutrient intakes (polyphenols, vitamin D, etc.) in health outcomes. We have the research tools and expertise need for such research endeavors. For instance, to our knowledge, we have at our disposal the most accurate polyphenol database, which includes 502 individual polyphenols from 452 different foods. It has already been merged with the SU.VI.MAX database, and is in the process of being merged with the NutriNet-Santé database. We have already started publishing on the topic in highly-respected journals (including publications on the links between polyphenols and cancer, polyphenol intake and cognition, polyphenols and weight change, etc.).
The launching of the NutriNet-Santé study online was one of the reasons to ensure the availability of a very large prospective cohort where cases of interest are of sufficient number. In addition, the issue of statistical power will not be of concern as regards the analyses. Finally, the recent authorization by the

State Council (dated 28 February 2013) will allow us to collect the NIR (social security number) and to have access to the national health care system database (SNIIRAM). These developments, in turn, will permit us to have access to accurate data regarding cancer sites, treatment, and recurrence.

Regarding the relationship between nutrition and "traditional" pathologies, we would like to underline the fact that many associations are still to be confirmed and/or clarified. Moreover, the mechanistic pathways by which nutritional factors intervene in cancerogenesis are still poorly understood. We are confident that our team has the skills and tools to be internationally competitive in this domain and to further scientific knowledge. We have already published a number of articles in the nutrition-cancer field in highly-respected journals (JAMA Intern Med (formerly Arch Intern Med), Am J Clin Nutr, Am J Epidemiol, etc.).
Further, compared to large traditional cohorts focused on the nutrition-cancer link, the NutriNet-Santé study presents several advantages, such as:

- High-quality, comprehensive assessment of nutritional intake via repeated 24h dietary records, supplemented with food frequency questionnaires and biomarker data. In addition, we are in a position to add ad hoc questionnaires depending on the exposures of interest. We also have expertise in variance reduction methods used in the assessment of usual nutrient intake, etc. In turn, several existing "traditional" cohorts rely on a single 24h dietary recall which is insufficient to accurately characterize nutritional exposures.
- Biobank with biological data from 20 000 participants, allowing us to perform analyses on nutritional biomarkers and to include mechanistic epidemiology approaches in our research. In addition, participants can be invited to undergo a biological examination "on demand," depending on ancillary protocols.
- Our team is a pioneer in the development/adaptation of high-quality food composition tables. To our knowledge, we have at our disposal the most accurate polyphenol database (Phenol-Explorer), which includes 502 individual polyphenols from 452 different foods. It has already been merged with the SU.VI.MAX database, and is in the process of being merged with the NutriNet-Santé database. We have already started publishing on the topic in highly-respected journals. We are also the first team internationally to publish findings derived from the Phenol Explorer database.
- Regarding case ascertainment, the validation of each major health event by an expert committee ensures the possibility to study accurately-defined pathologies (unlike data available from registries). For breast cancer, for instance, we record not only the cancer location, but also the histological type, the ER/PR receptor status, the parameters regarding invasiveness of the tumor, the number of nodes, etc.
  As presented in our report (and also during the oral evaluation), site-specific analyses will be performed to study the relationship between nutrition and cancer. In fact, we have already conducted such analyses (mostly for breast, prostate, skin, and colorectal cancer). This was also one of the reasons for launching the NutriNet-Santé study. This cohort allows us to study a large number of subjects followed during a long period of time. Thus, cancer incidence is expected to be relatively high (as calculated and explained in the study protocol). Furthermore, the recent authorization by the State Council (dated 28 February 2013) will allow us to collect the NIR (social security number) and to have access to the national health care system database (SNIIRAM). These developments are important as they will allow us to overcome limitations regarding, for example, loss to follow-up. The size of our cohort is entirely suitable in terms of statistical power for site-specific analyses – both for major cancer sites but also for rarer tumor locations.
  In turn, several existing cohorts focus only on one major pathology (eg, cancer or cardiovascular disease but not both), whereas we systematically record and validate all major pathologies in the same cohort. This allows us to have a good grasp of common and/or competitive risks as well as co-morbidities.
- Many well-established cohorts are now composed of relatively old participants whereas subjects of the NutriNet-Santé study are younger (ages 18+). This will allow us to study the relationship between nutrition and the onset of chronic diseases starting earlier in life.

- Our Internet tool allows us to easily collect information on any nutritional exposures that might become of interest in the near future (ie, it entails great adaptability).

4. Page 21, Conclusion, Recommendations, paragraph.1

> ***"The participation in international training programs could be a target in the future in order to improve international collaborations and the exchange of researchers"***

We share the assessor's view about the need to improve this point. We have just started discussions to develop an international training program in Nutritional Epidemiology with Imperial College London. Moreover, it is planned that in 2014 our team will be in charge of a module dedicated to e-epidemiology within the Master's program in Advanced Epidemiology established by Philippe Ravaud and Pierre Yves Ancel . It will be taught entirely in English by professors from the Universities of Paris Descartes and other Universities, as well as by international experts in epidemiology and will attract international students. Classes on Nutritional Epidemiology will be also given by members of the team in this Master's program.

5. Page 21, Conclusion, Recommendations, paragraph.2

> ***"The team should be proactive for cross-cutting research exchanges on nutrition within the Centre. There seems to exist a short-term opportunity to study nutrition during gestation (Team 1)"***

We fully agree with this recommendation. As we indicated in our oral presentation, we have planned to develop collaborations with Team 1 in the field of nutrition and pregnancy. Several meeting involving Team 1 and 3 researchers have been organized thus far to identify specific scientific questions of interest to both Teams. Some points of interest include the consumption of light foods, supplement use, evolution of dietary habits during pregnancy, role of specific nutrients, etc. The number of pregnant women in the NutriNet cohort has been assessed (about 7000 new pregnancies have been reported since the study was launched). This will permit us to develop ancillary protocols in this field.

One topic that we will address together with team 1 and which is of high public heath priority is the assessment of dietary supplement use during pregnancy. Indeed, some key nutrients (such as folic acid) should be consumed before and just at the beginning of pregnancy in order to prevent neural tube defects. In contrast, several arguments encourage caution regarding supplement use as self-medication during pregnancy for some nutrients. They pertain to the potential toxicity associated with overdose of some nutrients or bioactive compounds (such as retinol, vitamin E, phytoestrogens, etc.) and the potential deleterious effects of some herbal supplements, alone or when combined with medication use. Detailed data on dietary supplement use (and its determinants) during pregnancy is scarce internationally and no such data have been published for the situation in France, thus our collaboration with team 1 will bring brand new information regarding this important topic.

Team 2 will be join the discussions to upgrade statistical methods to study the relationship between nutrition (role of foods, nutrients, dietary behavior, physical activity) and gestation

6. Page 21, Conclusion, Recommendations, paragraph.3

> ***"The team should increase its expertise in novel statistical methods as well as in physical activity and sport sciences as it is an important emerging topic in the group (Team 2). As nutrition is more and more integrated in the lifestyle concept, the physical activity part should grow in the next years and probably will need some reinforcement.***

We fully agree that the physical activity component should be viewed in a comprehensive manner as regards lifestyle and health. This is in line with our interest in developing this specific research topic through the extension of our studies on methods to assess physical activity (and sedentary behavior)

and our studies on the geographical influences on the relationship between physical activity and health. Our collaboration with team 2 (Sylvie Chevret) would provide an opportunity to include advanced statistical modeling in this domain and upgrade our methods in terms of analysis plans. Specifically, we are working together with team 2 to upgrade our statistical skills regarding innovative missing data management, management and treatment of statistical data from metabolomics projects, inclusion of competitive risk parameters in our models, and improvement of our statistical methods for meta-analyses.
The physical activity component of our research agenda will be further strengthened by Didier Chapelot (MCF assistant Professor, section CNU 74, STAPS, Technical Sciences in Physical Activity and Sports) who will join our team in 2014.

7. Page 21, Conclusion, Recommendations, paragraph.4

> ***"The team should more clearly define research priorities in order to focus on innovative fields with high probability of outstanding publications, and develop an appropriate strategy for setting up projects with the other teams of the Centre.***

We fully agree that it is important to define the research priorities. As regards both the predictors of dietary behaviors and the link between diet/nutrition and health/disease, we will strive to advance knowledge and address major public health challenges. We will also develop and employ novel research tools (eg, a large e-cohort with detailed data on dietary exposures, physical activity, and health status). As regards the various specific study protocols (eg, cancer, CVD, metabolic conditions, cognition, etc.), our research tools allow us to approach these topic in an innovative manner (compared to existing cohorts on the international level which use conventional approaches). This strategy, coupled with the advanced statistical methodology to be employed as results of our collaborations within the Center will certainly help us augment the quantity and quality of our publications.

8. Page 21, Conclusion, Recommendations, paragraph.5

> ***"The committee recommends to pursue the discussions and coaching for a future leader of the team."***

As indicated under Factual Errors, it is planned that Serge Hercberg (PU-PH) will lead the team until the end of his term (2014-2018). Serge Hercberg will retire as University Professor in 2019. Neither Pr. Hercberg nor the members of team 3 plan on any leadership changes during the upcoming contract period. Given that Pr. Hercberg will retire as director at the end of the next term (2018), internal, preliminary discussions have indeed began and will continue during the next years. Two potential future leaders have been identified. They have been fully invested in the development of the research agenda for the upcoming contract. They have also contributed to the current responses to the comments in the AERES report. They will be progressively more involved in the life and in different aspects of the management of the Unit. They will be fully trained by the current Director. A collegial decision will be made in 2016 to choose the future leader who will be named as Assistant Director and will be ready to develop the future project of the Team. That person will be assisted by the other researchers and leaders of the different research axes.