"Process evaluation of population health intervention research: A complement or an alternative contribution to randomized controlled trial?"

International workshop on Intervention Research, Wednesday 16th of November 2016, Paris

Organization: Public Health Research Institute (IReSP), Alliance for life sciences and health (Aviesan), National Research Agency on AIDS and viral hepatitis (ANRS), National Cancer Institute (INCa)

A Need of NPI Ontology for Intervention Research

Pr. Grégory Ninot,

Gérard Bourrel, François Carbonnel, Aurélie Gerazime, Estelle Guerdoux-Ninot, Thérèse Libourel, Béatrice Lognos, Jérome Maitre, Jeanne Michaux, Loc The Nguyen, Sylvie Rapior, Raphael Trouillet, Anne Laurent

Executive Director of CEPS Plateform

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www.CEPSplatform.eu

Co-Director Human Sciences Topic / Supportive Care

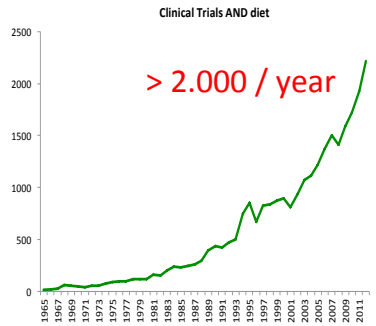
SIRIC MONTPELLIER CANCER

Site de Recherche Intégrée sur le Cancer

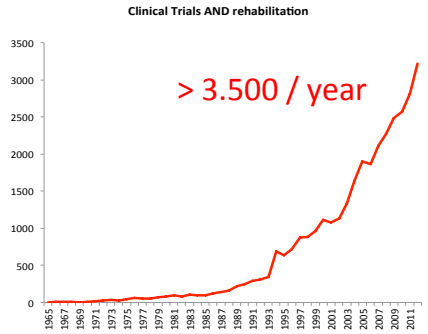
www.montpellier-cancer.com

Context

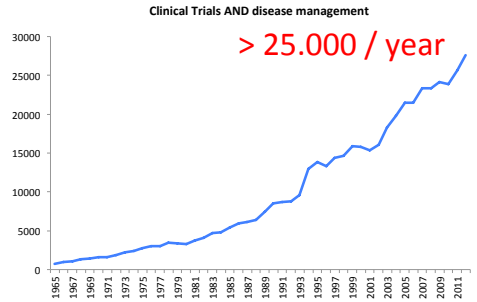
An exponential increase of NPI trial publications since 20 years



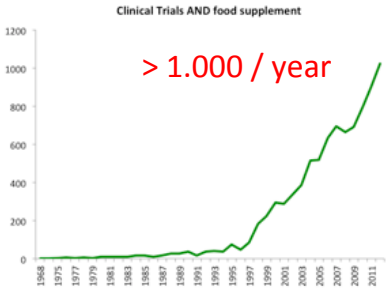
Diet programs



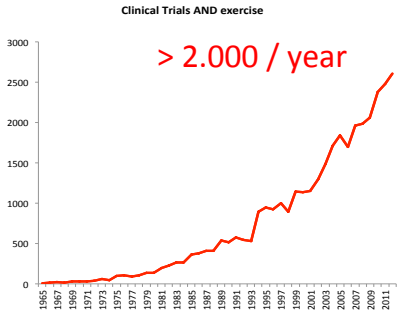
Physiotherapy methods



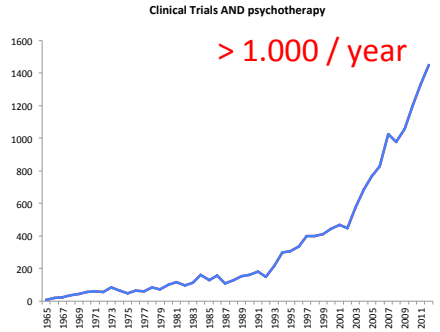
Disease management programs



Food supplements



Exercise programs



Psychoterapies

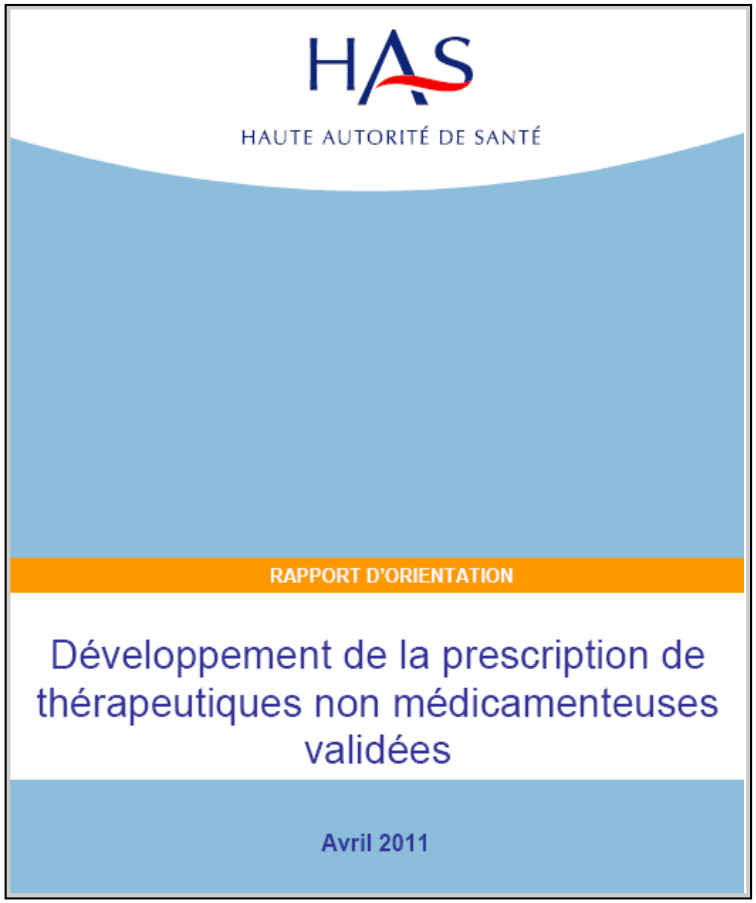
2 millions since 1827, **73.691** in 2014 (only on Pubmed Database, 2015)

One example among many

"These findings are open to criticism because of the ***notable heterogeneity*** *across the included studies and the shortcomings of the included studies."*

Jassim *et al.* (2015, *Cochrane Database Systematic Review*)

Health Authorities are still waiting for evidence of efficacy



"**In light of the standards usually applied to evaluate the efficacy of medical treatments**, most studies assessing the efficacy of non-pharmacological therapies [*hygiene and dietary practices, psychological treatments, physical therapies*] suffer from **methodological weaknesses**."

French Health Authority – HAS (April 2011, p.40)

HAS (2011)

A need of high quality trials

OPEN ACCESS Freely available online

PLOS | MEDICINE

Essay

How to Make More Published Research True

John P. A. Ioannidis[1,2,3,4]*

1 Meta-Research Innovation Center at Stanford (METRICS), Stanford University, Stanford, California, United States of America, **2** Department of Medicine, Stanford Prevention Research Center, Stanford, California, United States of America, **3** Department of Health Research and Policy, Stanford University School of Medicine, Stanford, California, United States of America, **4** Department of Statistics, Stanford University School of Humanities and Sciences, Stanford, California, United States of America

"**many published research findings are false or exaggerated**, and an estimated 85% of research resources are wasted" (p.1)

Adoption of more appropriate statistical methods [38], standardized definitions and analyses and more stringent thresholds for claiming discoveries or "successes" [39] may decrease false-positive rates in fields that have to-date been too lenient (like epidemiology [40], psychology [41,42], or economics [43]). It may lead them to higher credibility, more akin to that of fields that have traditionally been more rigorous in this regard, like the physical sciences [44].

Ioannidis (2015, *Plos Medicine*)

Example:
Exercise and cancer

Exercise and cancer

1986

2016

Exercise and cancer

Need to be integrated in every "parcours de soin" (Plan Cancer III 2014-2019)

« La place de la prévention destinée aux personnes ayant eu un cancer sera accrue. L'accompagnement au sevrage tabagique des patients sera ainsi systématisé et mieux pris en charge, ainsi que les démarches favorisant la réduction de la consommation d'alcool, la pratique d'une activité physique adaptée et une alimentation équilibrée » [p.11, Plan Cancer III].

Need to be prescribed (amendement Fourneyron 2015)

Après l'article L. 1142-29 du code de la santé publique, il est inséré l'article L. 1142-30 :
« Art. 1142-30. – Dans le cadre du parcours de soins des patients atteints d'une maladie de longue durée, le médecin traitant peut prescrire une activité physique adaptée à la pathologie, aux capacités physiques et au risque médical du patient. »

New French recommendations in 2017 (collective expertise)

INSTITUT NATIONAL DU CANCER Inserm HAS HAUTE AUTORITÉ DE SANTÉ

Exercise program and cancer

Content (theory, techniques)?

Dose (frequency, intensity, period)?

Supervision or not?

During or after conventional treatments (surgery, chemotherapy and radiotherapy)?

Equivalence for Efficacy and Safety?

Belief propagated extensively by the Media and the Internet

Making patients more less naïve…

… but paradoxically, more vulnerable to:

- **abuse (e.g., sects, dangerous practices, etc.),**
- **misinformation (e.g., marketing vs. science).**

Exercise and cancer

Alternatives to treatments?

Science & Vie
(January, 2015)

Time Magazine
(October, 2015)

Exercise and cancer

No citations in an official patient guideline

Guide of French League Against Cancer (2013)

One step:
A need of Non-Pharm Interventions Ontology

Efficacy of exercise on perceived fatigue during breast cancer treatments

Annals of Oncology 24: 291–300, 2013
doi:10.1093/annonc/mds342
Published online 5 October 2012

Psychological effect of exercise in women with breast cancer receiving adjuvant therapy: what is the optimal dose needed?

M. Carayol[1,2*], P. Bernard[1], J. Boiché[1], F. Riou[1], B. Mercier[1], F. Cousson-Gélie[1], A. J. Romain[1], C. Delpierre[2] & G. Ninot[1]

[1]*Laboratory Epsylon EA 4556 Dynamics of Human Abilities and Health Behaviors, University of Montpellier, Montpellier;* [2]*INSERM UMR 1027, Paul Sabatier University, Toulouse, France*

Received 3 February 2012; revised 13 July 2012; accepted 16 July 2012

Carayol *et al.* (2013, *Annals of Oncology*)

Psycho-Oncology
Psycho-Oncology (2014)
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI**: 10.1002/pon.3727

Review Article

Population-, intervention- and methodology-related characteristics of clinical trials impact exercise efficacy during adjuvant therapy for breast cancer: a meta-regression analysis

Marion Carayol[1,2*], Cyrille Delpierre[2], Paquito Bernard[1] and Grégory Ninot[1]
[1]*Laboratory Epsylon EA 4556 Dynamics of Human Abilities and Health Behaviors, University of Montpellier, Montpellier, France*
[2]*INSERM UMR 1027, Paul Sabatier University, Toulouse, France*

Carayol *et al. (*2014, *Psycho-Oncology*)

Difficulties to characterize intervention

A need to describe interventions

knowledge, no study has yet made a head-to-head comparison of these two types of programs.

The primary aim of our study was to evaluate the effectiveness of a home-based, low-intensity physical activity program (Onco-Move) and a supervised, moderate- to high-intensity, combined resistance and aerobic exercise program (OnTrack) in maintaining or enhancing physical fitness and minimizing fatigue in patients undergoing adjuvant chemotherapy. In addition, we hypothesized that both interventions would result in higher levels of physical activity and functioning in daily life, less psychological distress, and better HRQoL. We expected greater gains in cardiorespiratory fitness and muscle strength for participants in the OnTrack versus the Onco-Move program. Finally, we hypothesized a positive effect of both interventions on chemotherapy completion rates (ie, the percentage of patients who would complete chemotherapy without dose adjustments).

PATIENTS AND METHODS

Research Design and Study Sample

The Physical Exercise During Adjuvant Chemotherapy Effectiveness Study (PACES) was a randomized, controlled, multicenter trial with two intervention groups and a usual care (UC) control group. Patients were eligible for the trial if they had histologically confirmed primary breast or colon cancer and were scheduled to undergo adjuvant chemotherapy at one of 12 hospitals in the Amsterdam region of the Netherlands.[14] Patients were excluded if they had serious orthopedic, cardiovascular, or cardiopulmonary conditions, were suffering from malnutrition, had serious psychiatric or cognitive problems, or did not have basic fluency in Dutch. There was no upper age limit. Institutional review boards of all participating hospitals approved the study.

Procedure

Potentially eligible patients with breast cancer were identified through hospital records, whereas patients with colon cancer were identified by their treating physicians. After providing informed consent and completing baseline assessments, patients were randomly assigned to Onco-Move, OnTrack, or UC using the minimization method,[15] which balanced groups with respect to age, primary diagnosis, treating hospital, and use of trastuzumab.

Interventions

Onco-Move is a home-based, low-intensity, individualized, self-managed physical activity program, as proposed by Mock,[12] to which behavioral reinforcement techniques were added in this study. These comprised written information that was tailored to the individual's preparedness to exercise according to the Transtheoretical model,[16] and an activity diary that was discussed at each chemotherapy cycle. Specially trained nurses encouraged participants to engage in at least 30 minutes of physical activity per day, 5 days per week, with an intensity level of 12 to 14 on the Borg Scale of perceived exertion.[17]

OnTrack is a moderate- to high-intensity, combined resistance and aerobic exercise program and was supervised by specially trained physical therapists.[18] The participants attended two sessions per week. Six large muscle groups were trained for 20 minutes per session, with two series of eight repetitions at 80% of the one repetition maximum. One repetition maximum testing was repeated every 3 weeks. Each session incorporated 30 minutes of aerobic exercises, with an intensity of 50% to 80% of the maximal workload as estimated by the Steep Ramp Test.[19] The intensity was adjusted using the Borg Scale, with a threshold of less than 12 for increase and more than 16 for decrease of intensity.[17] Participants in this group were also encouraged to be physically active 5 days each week for 30 minutes per session and to keep an activity diary. Both interventions started with the first cycle of chemotherapy and continued until 3 weeks after the last cycle.

UC varied according to hospital guidelines and preferences, but did not involve routine exercise.

Timing of Assessments and Study Measures

Patients underwent performance-based tests and completed questionnaires at three points in time: before random assignment and start of chemotherapy (T0), at completion of chemotherapy (T1), and 6 months after completion of chemotherapy (T2).

Primary outcomes were cardiorespiratory fitness, muscle strength, and fatigue. Cardiorespiratory fitness was assessed with the Steep Ramp Test[19] and an endurance test at 70% of the estimated maximal workload.[14] muscle strength with the microFET handheld dynamometer (Hoggan Health, Salt Lake City, UT) for elbow flexion[20] and knee extension,[21] and the JAMAR grip strength dynamometer (Lafayette Instrument, Lafayette, IN),[22] and lower-limb muscle endurance with the 30-second chair stand test.[23] Fatigue was measured with the Multidimensional Fatigue Inventory[24] and the Fatigue Quality List.[25]

The secondary outcomes included self-reported physical activity level, functioning in daily life, psychological distress, HRQoL, return to work, and chemotherapy completion rates[14,26] (Table 1).

Statistical Analyses

With more than 64 participants per group, the study had 80% power to detect an effect size of 0.5, with a two-tailed *P* value set at .05.[27] Scores on the Multidimensional Fatigue Inventory, Fatigue Quality List, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), Hospital Anxiety and Depression Scale, Sleep Quality Inventory, Impact on Participation and Autonomy, and Physical Activity Scale for the Elderly were calculated according to published scoring algorithms.

Table 1. Outcome Measures

Assessment	Measurement Instrument
Primary outcome measures	
Cardiorespiratory fitness	Steep Ramp Test: maximal short exercise capacity
	Endurance test, endurance time
Upper muscle strength	MicroFET† handheld dynamometer elbow flexion, Nm
	JAMAR* grip strength dynamometer, kg
Lower muscle strength	MicroFET† handheld dynamometer knee extension, Nm
	30-second chair stand test: No. of times to rise
Fatigue	Multidimensional Fatigue Inventory
	Fatigue Quality List
Secondary outcome measures	
Health-related quality of life	EORTC QLQ-C30
Psychological distress	Hospital Anxiety and Depression Scale
Self-reported physical activity level	Physical Activity Scale for the Elderly
Functioning in daily life	Impact on Participation and Autonomy
Quality of sleep	Sleep Quality Inventory
Return to work	Return to work questionnaire (study specific)
Chemotherapy regimen, dose, and adverse effects of chemotherapy	Medical records
Compliance with exercise programs	No. of sessions attended
	Activity diary
Other measures	
Clinical characteristics	Tumor stage and type (medical records)
	Radiotherapy (yes v no; medical records)
	Comorbidity (questionnaire)

Abbreviation: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30.
*Lafayette Instrument, Lafayette, IN.
†Hoggan Health, Salt Lake City, UT.

VOLUME 33 · NUMBER 17 · JUNE 10 2015

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial

Hanna van Waart, Martijn M. Stuiver, Wim H. van Harten, Jacobien M. Kieffer, Marianne de Maaker-Berkhof, Gabe S. Sonke,

Hanna van Waart, Martijn M. Stuiver, Wim H. van Harten, Edwin Geleijn, Jacobien M. Kieffer, Laurien M. Buffart, Marianne de Maaker-Berkhof, Epie Boven, Jolanda Schrama, Maud M. Geenen, Jetske M. Meerum Terwogt, Aart van Bochove, Vera Lustig, Simone M. van den Heiligenberg, Carolien H. Smorenburg, Jeannette A.J.H. Hellendoorn-van Vreeswijk, Gabe S. Sonke, and Neil K. Aaronson

Van Waart *et al.* (2015, *Journal of Clinical Ontology*)

CONSORT TRANSPARENT REPORTING of TRIALS

Annals of Internal Medicine | ACADEMIA AND CLINIC

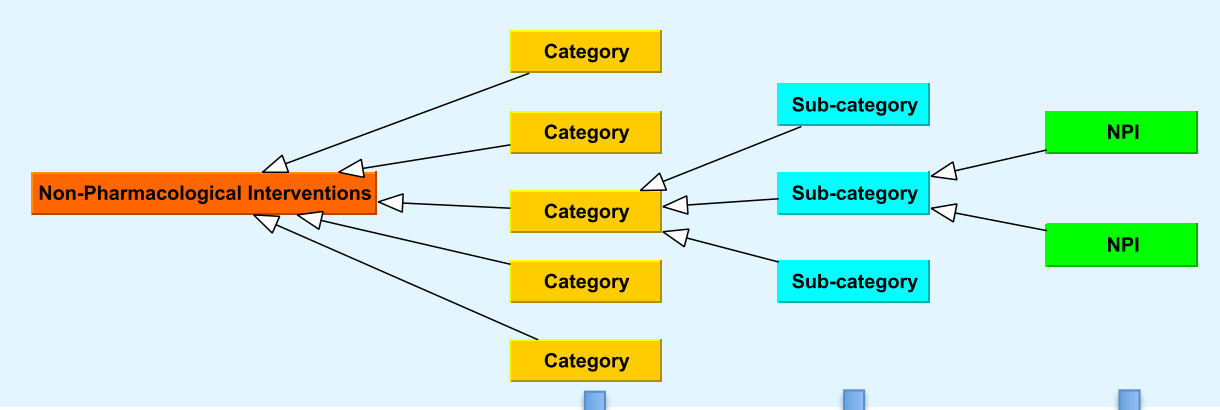
Extending the CONSORT Statement to Randomized Trials of Nonpharmacologic Treatment: Explanation and Elaboration

Isabelle Boutron, MD, PhD; David Moher, PhD; Douglas G. Altman, DSc; Kenneth F. Schulz, PhD, MBA; and Philippe Ravaud, MD, PhD, for the CONSORT Group*

Boutron *et al.* (2008, *Annals of Internal Medicine*)

Decomposition of one NPI following a top-down approach

A need of a collaborative NPI ontology

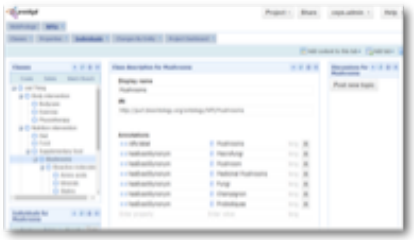


Psychological Health Intervention
(and synonyms)

Psychotherapy
(and synonyms)

Mindfulness-Based Stress Reduction
(and synym e.g. MBSR)

for developing the ontology



WebProtégé

Selected tools

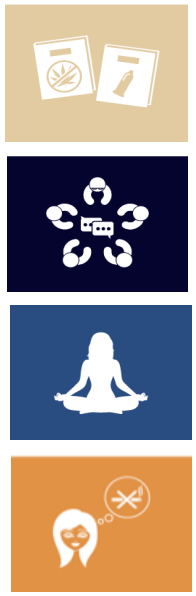
+

BioPortal

for sharing the ontology

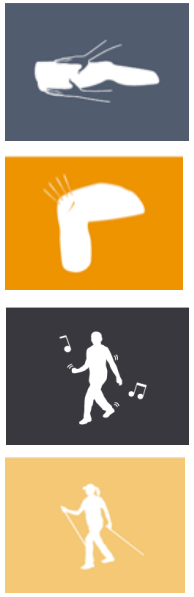
www.cepsplatform.eu

A need of a collaborative NPI ontology



Psychological Health Interventions

(from prevention programs to psychotherapy methods)

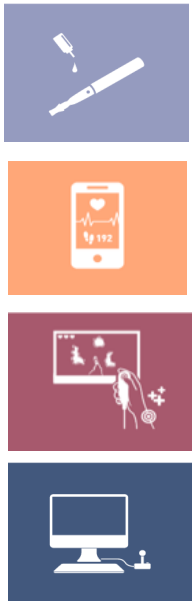


Body Health Interventions

(from manual therapies to adapted physical activity programs)

Nutritional Health Interventions

(from diet supplements to therapeutic diets)



Digital Health Interventions

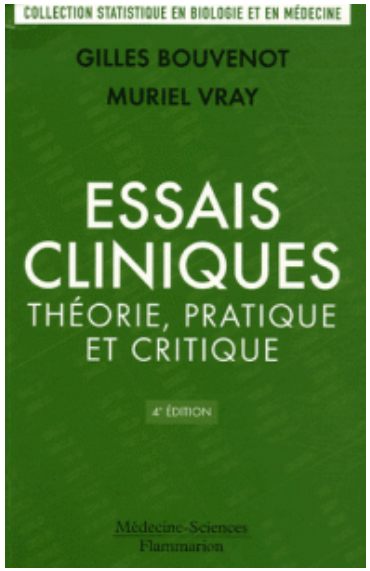
(from e-health devices to health e-coaching solutions)

Other Health NP Interventions

(from phytotherapy to aromatherapy)

Conclusion

Non-Pharmacological Interventions (NPIs), as drug 50 years ago



«Until the 60's, many drug interventions only relied, we might say, on the strength of habit (routine), a **naive belief** in traditions, or on generalizations made on the basis of anecdotal and sporadic instances abusively labeled as professional experience. .»

Bouvenot (2006, p.XIII)

CEPS PLATFORM

Improving the quality of NPI trials

Curr Cardiovasc Risk Rep (2015) 9:427
DOI 10.1007/s12170-014-0427-0

PHYSICAL ACTIVITY (D WARBURTON, SECTION EDITOR)

An International Perspective on Improving the Quality and Potential of Behavioral Clinical Trials

Simon L. Bacon · Kim L. Lavoie · Gregory Ninot · Susan Czajkowski · Kenneth E. Freedland · Susan Michie · Paul Montgomery · Lynda H. Powell · Bonnie Spring · for the International Behavioural Trials Network (IBTN)

ibtn
international
behavioural
trials network

Bacon *et al.* (2015, *Curr Cardiovasc Risk Rep*)

A International conference on NPI research

Edition n°1
Montpellier
March 25, 2011

1 day
320 participants
6 plenaries
6 workshops

Edition n°2
Montpellier
April 5, 2013

1 day
610 participants
11 plenaries
6 workshops

Edition n°3
Montpellier
March 19-21, 2015

3 days
1030 participants
35 plenaries
11 workshops
68 posters

Edition n°4
Montréal
May 19-21, 2016

3 days
250 participants
30 plenaries
10 workshops
29 posters

www.iceps.eu

ICEPS Conference 2017, Montpellier

www.iceps.eu

Thank you for your attention

CEPS PLATFORM

European Methodology Plateform for Non-Pharmacological Intervention Research

Universities of Montpellier, France

www.CEPSplatform.eu