IMI-PainCare

Improving the care of patients suffering from acute or chronic pain

PROMPT

BioPain

TRiPP

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imi innovative medicines initiative efpia

IMI-PainCare

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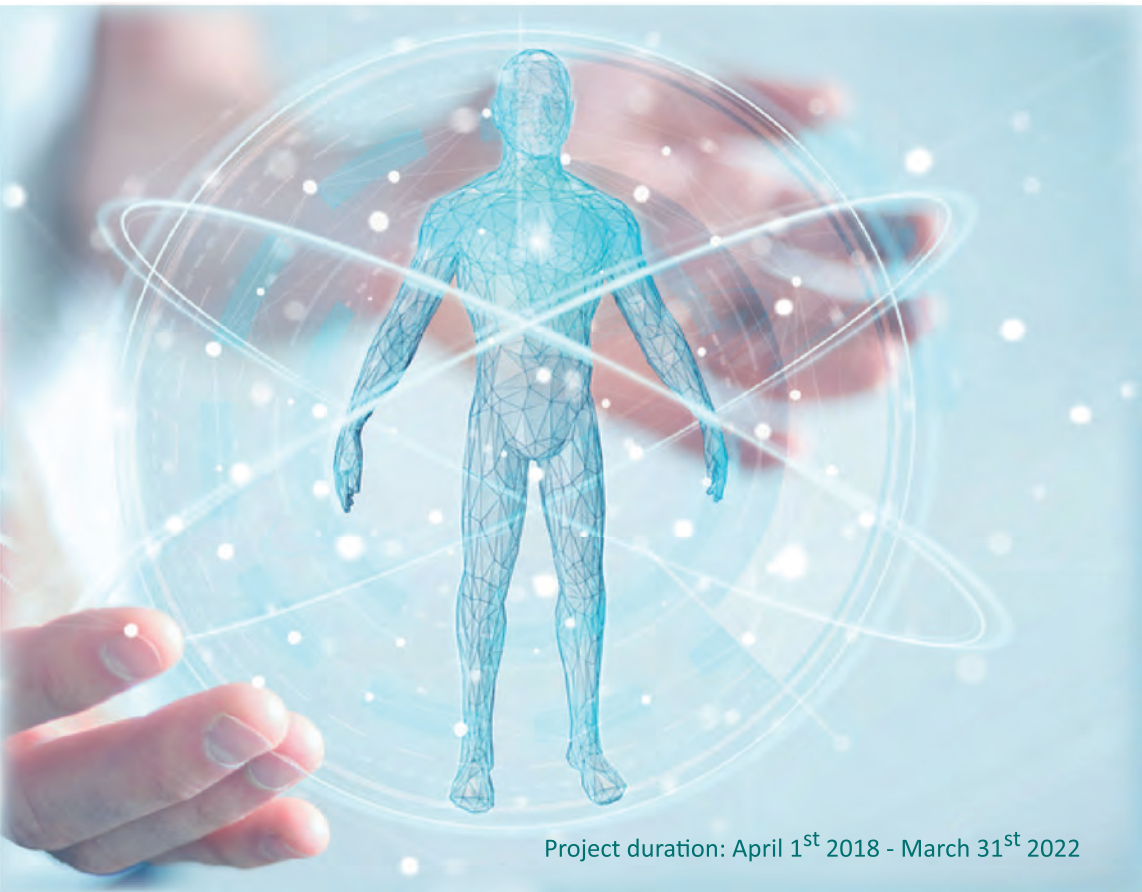
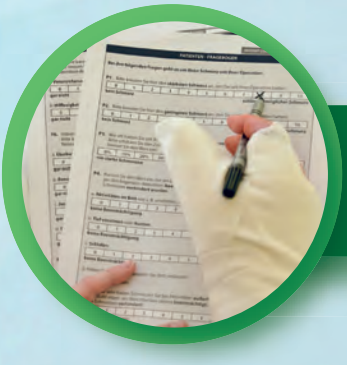


Project duration: April 1st 2018 - March 31st 2022

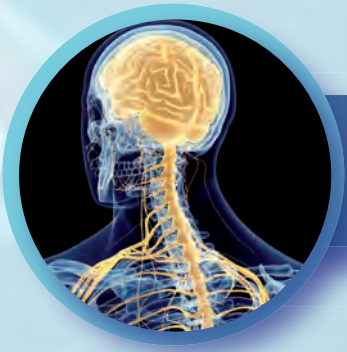
Acknowledgement:
This project has received funding from the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking under grant agreement No: 777500. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.
More information about IMI2: www.imi.europa.eu.

This project comprises three sub-projects:



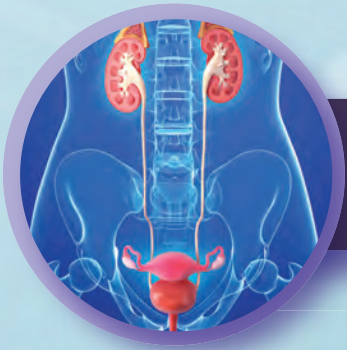
PROMPT

Providing Standardized Consented Patient Reported Outcome Measures (PROMs) for Improving Pain Treatment



BioPain

Improving translatability of functional biomarkers in pain pathwas



TRiPP

Improving translation in chronic pelvic pain

Overview of the project and the public-private consortium

Expected outcomes:

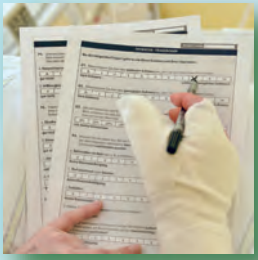
(1) Alignment on outcomes in acute post-operative and chronic pain (follow-up of treatment success in clinical practice, clinical trials for drug development)

(2) Refining preclinical pain models and enhancing their translation into the clinic

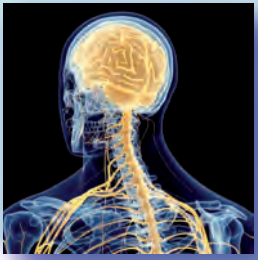
(3) Providing new approaches for patient stratification in clinical trials

(4) Identification of translatable pharmacodynamic biomarkers to prove target engagement in the clinical development of new analgesics

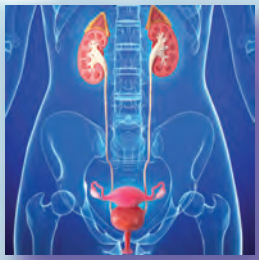
(5) Supporting decision making in clinical practice



PROMPT

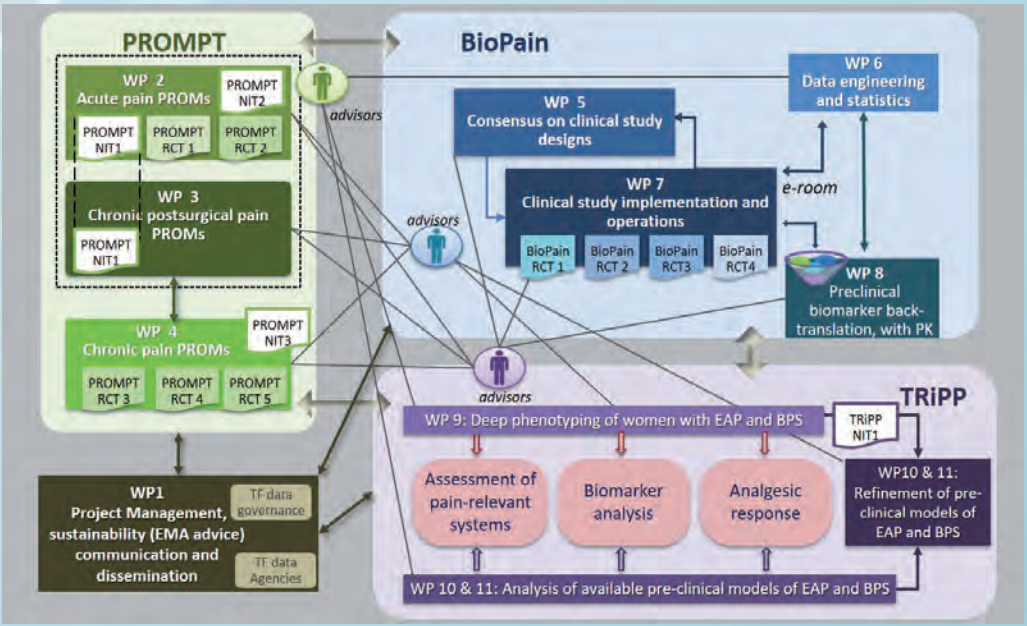


BioPain



TRiPP

Whereas the three sub-projects address distinct aspect and scientific challenges, bringing them together into one project creates the opportunity for valuable cross-fertilization between them.



IMI-PainCare

PROMPT Providing Standardized PROMs For Improving Pain Treatment

Providing Standardized Patient Reported

It's All About Pain Measurement

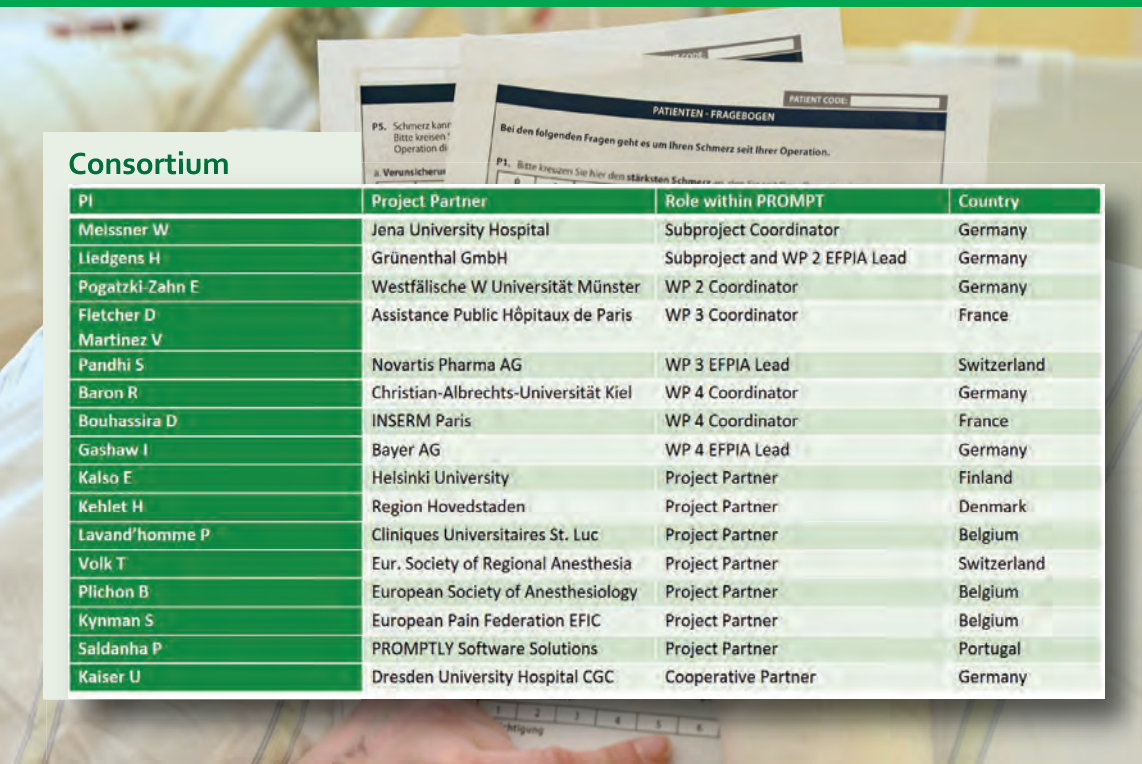
PROMPT seeks to improve the management of acute and chronic pain by identifying a core set of Patient Reported Outcome Measures (PROMs) which are predictive indicators of treatment success in clinical practice and controlled trials.

These will address pain intensities as well as the functional consequences of pain for individuals, and identify patients at risk of experiencing chronification of acute post-operative pain. This will help health care professionals to individualize pain management, and thus improve the quality of life of pain patients.

Furthermore, the correlation of baseline characteristics and a selection of PROMs for specific chronic pain conditions will identify which parameter(s) most reliably predict treatment success.

Workpackages:

WP 2: Acute Pain PROMs
WP 3: Chronification PROMs
WP 4: Chronic Pain PROMs
Email: Prompt@med.uni-jena.de



Consortium

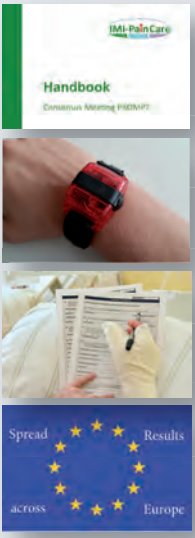
PI	Project Partner	Role within PROMPT	Country
Meissner W	Jena University Hospital	Subproject Coordinator	Germany
Liedgens H	Grünenthal GmbH	Subproject and WP 2 EFPIA Lead	Germany
Pogatzki-Zahn E	Westfälische W Universität Münster	WP 2 Coordinator	Germany
Fletcher D Martinez V	Assistance Public Hôpitaux de Paris	WP 3 Coordinator	France
Pandhi S	Novartis Pharma AG	WP 3 EFPIA Lead	Switzerland
Baron R	Christian-Albrechts-Universität Kiel	WP 4 Coordinator	Germany
Bouhassira D	INSERM Paris	WP 4 Coordinator	France
Gashaw I	Bayer AG	WP 4 EFPIA Lead	Germany
Kalso E	Helsinki University	Project Partner	Finland
Kehlet H	Region Hovedstaden	Project Partner	Denmark
Lavand'homme P	Cliniques Universitaires St. Luc	Project Partner	Belgium
Volk T	Eur. Society of Regional Anesthesia	Project Partner	Switzerland
Plichon B	European Society of Anesthesiology	Project Partner	Belgium
Kynman S	European Pain Federation EFIC	Project Partner	Belgium
Saldanha P	PROMPTLY Software Solutions	Project Partner	Portugal
Kaiser U	Dresden University Hospital CGC	Cooperative Partner	Germany

Outcome Measures for Improving Pain Treatment (PROMPT)

PROMPT Objectives in a Nutshell

- Identifying PROMs that work best for assessing and following-up acute postop pain
- Identifying PROMs that are indicative for chronification of acute postop pain
- Developing a Predictor of Chronic Pain
- Identifying PROMs indicative of treatment success in chronic neuropathic and pelvic pain conditions

That's How We Will Do It



pictures: UKJ

- Reaching a consensus on a core set of PROMs by a formal DELPHI process
- Systematic literature reviews to identify suitable PRO domains and measures
- Applying these PROMs in prospective data collection studies and RCTs in postoperative patients
- Analysis of PROMs in EFPIA studies on acute + chronic pain
- Development of a Chronic Pain Predictor (CPP)
- Dissemination of results to foster use of the PROMs in clinical routine

Studies in PROMPT

Data from different non-interventional studies (NITs) and RCTs will be assessed for finding the most suitable PROMs. PROMPT will use data from both, historic and pospectively collected data. A large multicenter prospective data collection will assess postop pain after TKA, sternotomy, breast surgery and endometriosis related surgery.
This study will include a follow-up of 4,000 patients after 1, 3, and 6 months.
By use of activity trackers, patients' movements and sleep patterns will be monitored to assess functional consequences of pain and their potential impact on chronification.

Expected Outcomes

Improvement of pain management by use of consented, standardized PROMs that are accepted around the world

Improving translatability of functional biomarkers in pain pathways (BioPain)

Chronic pain is a major cause of years lived with disabilities and loss of productive work time. Analgesic drug development has been stagnant in the past decade because results of preclinical studies often fail to predict those of clinical trials. BioPain aims to close this translation gap by standardizing and pharmacologically validating objective measures of nociceptive signalling that translate between animals and humans.

We will perform four RCTs in healthy subjects and parallel trials in rats using electrophysiological and imaging biomarkers of peripheral, spinal and brain signal processing. (June 2021)

We will use pharmacokinetic/pharmacodynamic (PK/PD) modelling to delineate the actions of standard-of-care drugs in these neural compartments. (December 2021)

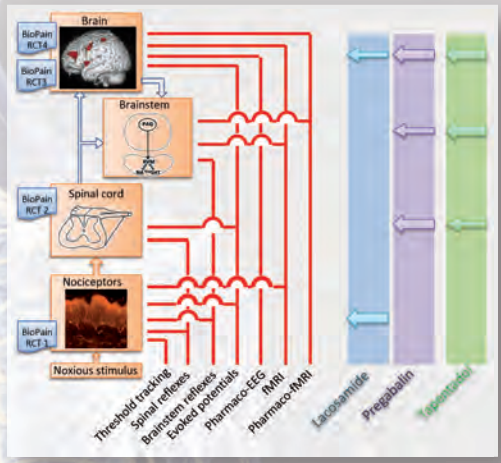
We will also record pain intensity, distress and anxiety.

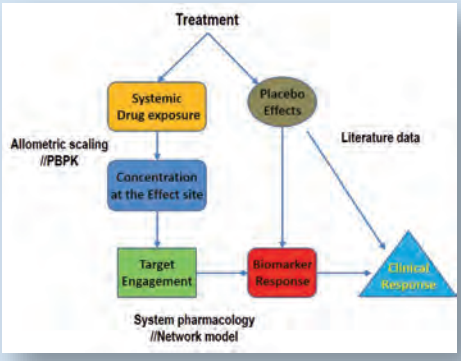
This way we will provide tools necessary to implement patient stratification and enrichment as encouraged by the EMA/CHMP/970057/2011 guideline.

Concept and approach of BioPain

Key compartments of nociceptive pathways (periphery,spinal cord, brainstem, brain) are accessible through a network of electrophysiological and imaging biomarkers.
Current analgesic drugs typically act on more than one compartment. Novel study designs and complex analysis techniques are proposed to disentangle these networks.
The three drugs and seven biomarkers listed are examples of those under consideration.

Reference : Treede RD (2016) Gain control mechanisms in the nociceptive system. Pain 157: 1199-12



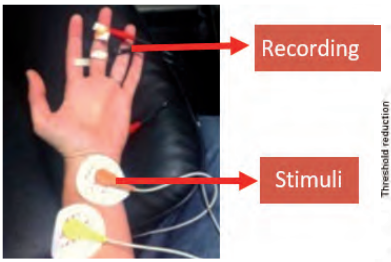


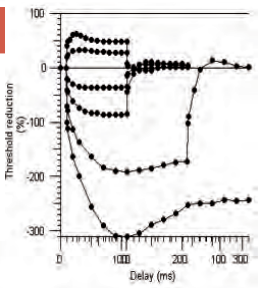
A pharmacokinetic/pharmacodynamic (PK/PD) approach to data analysis will enable the time course of concentration effect to be studied and enable better translation between rat and human.

The proposed approach will incorporate:

- Inter-species PK scaling (allometric or PBPK)
- Mechanistic approaches to PK/PD to evaluate signal propagation and aid inter-species translation (systems pharmacology/networkanalysis)
- Elucidation of placebo effects

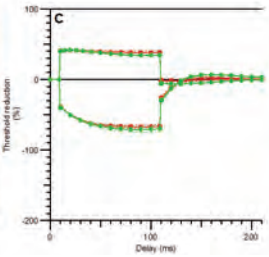
Peripheral Biomarkers





Humans: threshold tracking

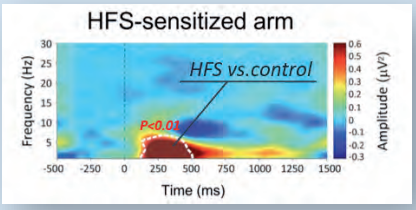
Reference : Serra et al. unpublished data



Rats: threshold tracking

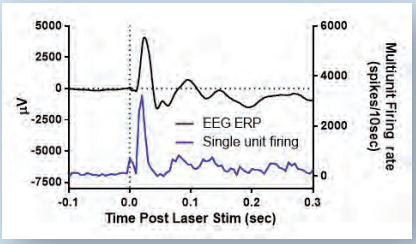
Reference : Phillips et al. unpublished data

Brain biomarkers



Humans: stimulus-evoked brain potentials and pharmaco-EEG. Time frequency analysis of noci-ceptive pinprick-evoked potentials with and with-out prior induction of central ensitization using high-frequency stimulation of the skin (HFS).

Reference : van den Broeke et al., Clin Neurophysiol (2017)



Rats: Example of depth local-field potentials (black) in combination with single-unit recordings (blue) recorded in the primary somato-sensory cortex

Reference : Phillips et al. unpublished data

Consortium

Main contacts and WP-leads	Project Partner	Country
Treede RD, Caspani O, Kostenko A	Heidelberg University	Germany
Finnerup N, Tankisi H	Aarhus University	Denmark
Schubart D, Wirtz U, Schubart K	ConsulTech GmbH	Germany
Garcia-Larrea L	National Institute of Health and Medical Research	France
Goetz M, Pelz B	MRC Systems GmbH	Germany
Serra J, Solà R	Neuroscience Technologies SLP	Spain
Truini A, Cruccu G, Distefano G	Sapienza University Rome	Italy
Mouraux A, Stouffs A, Lebrun L	Universite Catholique de Louvain	Belgium
Trocóniz I, Marco N	University of Navarra	Spain
Tracey I, Wanigasekera V, Ho I	University of Oxford	United Kingdom
Phillips K, Tate SC, Blockeel A	Eli Lilly	United Kingdom
Blohms-Funke P, Schuckelt A, Boesl I, Winkel M	Grunenthal GmbH	Germany
Cendros M, Vela M, Merlos M	Esteve Pharmaceuticals S.A.	Germany
Yoetz T, Snider S	Teva	Israel

Expected Outcomes

(1) Refining preclinical pain models and enhancing their translation into the clinic

(2) Identification of translatable pharma-codynamic biomarkers to prove target engagement in the clinical development of new analgesics

Summary statement:

standardization and pharmacological validation towards accelerated translation in analgesic drug development

Translational Research in Pelvic Pain

Although chronic pelvic pain is as common as asthma, migraine and back pain, and has very negative impacts on life quality, it remains a neglected field of research. The most common chronic pelvic pain is endometriosis associated pain (EAP); current treatments are limited to repeated surgeries or hormone suppression therapies which are often ineffective.
Another recognised type of chronic pelvic pain, bladder pain syndrome (BPS), has a far lower prevalence (ca. 0.06%), but is also associated with strongly reduced life quality and significant psychological distress. Current treatments target the bladder, but are as unsuccessful as those for EAP. As there are currently no non-invasive functional or biochemical biomarkers, unambiguous diagnosis of both conditions requires surgery.
Comorbidities such as autoimmune, endocrine and other pain conditions are common amongst EAP and BPS sufferers, and may confuse clinical evaluations and studies of the underlying causes of either condition. Development of novel effective therapies has been hindered by the lack of preclinical models which reflect the full range of clinical symptoms. Subproject TRiPP will advance the field by adopting new approaches to stratify patients by underlying mechanistic pathways, which leverage cross-disciplinary knowledge of pain mechanisms with state-of-the-art biomarker discovery, and then to develop and optimise preclinical disease models.

Endometrosis

- Hormone-dependent growth of uterine epithelial tissue outside the uterine cavity
- Highly prevalent disease, 5-10% of all women in reproductive age
- Limited disease understanding

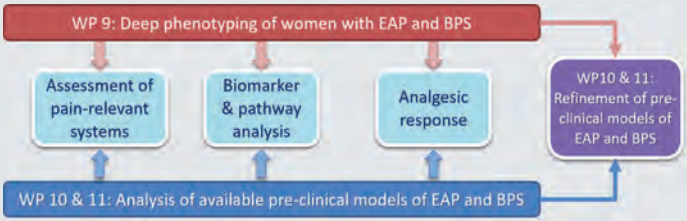
BPS/IC

- Chronic bladder voiding condition of unknown aetiology
- Highly prevalent disease affecting both gender, up to 7% of women in Western countries
- Common clinical symptoms are urinary frequency, nocturia, and pelvic pain

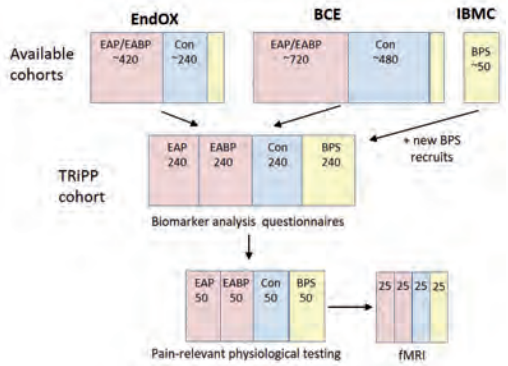
Overview of PIs and partners

PI	Project Partner	Role within TRiPP	Country
Vincent K	University of Oxford	Subproject coordinator, WP9 lead	United Kingdom
Zondervan K	University of Oxford	Omics lead	United Kingdom
McMahon S	King's College London	WP11 lead	United Kingdom
Saunders P	University of Edinburgh	WP10 lead	United Kingdom
Cruz F	Instituto de Biologia Molecular e Celular, Porto	BPS clinical lead	Portugal
Gomez R	Fundacion para la Investigacion del Hospital Clinico de la Comunitat Valenciana	Project Partner	Spain
Aziz Q	Queen Mary's University, London	Project Partner	United Kingdom
Arendt-Nielsen L	University of Aalborg	Project Partner	Denmark
Birch J	Pelvic Pain Support Network	Project Partner	United Kingdom
Hummelshoj L	Endometriosis.org Ltd	Project Partner	United Kingdom
Meijlink J	International Painful Bladder Foundation	Project Partner	Netherland
Armstrong D	Actual Analytics	Project Partner	United Kingdom
Missmer S	Michigan State University	Project Partner	USA
Sieberg C	Boston Children's Hospital / Harvard Medical School	Project Partner	USA
Nagel J	Bayer AG	Subproject lead, WP9 lead	Germany
Tzschentke T	Grünenthal GmbH	WP10 lead	Germany
Roca M M	Esteve Pharmaceuticals S.A	WP11 lead	Spain

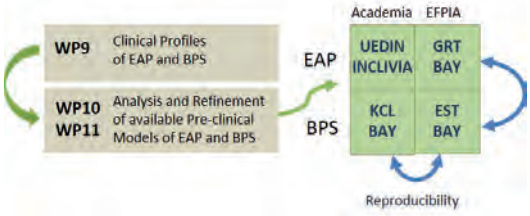
Concept and approach of TRiPP



Findings from deep phenotyping of women with two CPP-syndromes (mainly including large existing cohorts) will be compared with existing pre-clinicalmodels to refine the pre-clinical models for better mechanistic and prospective validity.



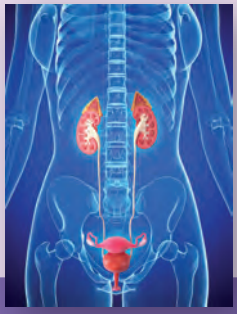
Workpackages



Flowchart clinical study Available cohorts: EndOx. Oxford; BCE: Harvard; IBMC: Porto

Outline of proposed biospecimen analysis, existing data and additional sample availability

Subgroup	Profiling in blood (serum/plasma)	Profiling in tissue (eutopic/ectopic endometrium)	Additional available data*	Additional samples available for targeted follow-up
EAP n=200	Metabolomics, Proteomics	Proteomics, Transcriptomics (n=120)	Genomics, Transcriptomics	Urine, saliva, peritoneal fluid, eutopic/ectopic endometrium
BPS n=200	Metabolomics, Proteomics		(Genomics)[£]	Urine, saliva, bladder biopsies
EABP n=200	Metabolomics, Proteomics		Genomics, Transcriptomics	Urine, saliva, peritoneal fluid, eutopic/ectopic endometrium
Controls n=200	Metabolomics, Proteomics	Proteomics, Transcriptomics (n=120)	Genomics, Transcriptomics	Urine, saliva, peritoneal fluid, eutopic endometrium



Expected outcomes:

- Provide deeper understanding of the pathological conditions which lead to pelvic pain
- Deep phenotyping of women with these two CPP-syndromes will be performed
- Existing pre-clinical models will be assessed and then refined in line with the clinical phenotypes aiming for better mechanistic and predictive validity

Summary statement:

Increase disease understanding of EAP and BPS leading to patient stratification and improvement of preclinical model validity

The public-private consortium

The IMI-PainCare Consortium is composed of 40 participants from14 countries; 6 are EFPIA members (European Federation of Pharmaceutical Industries and Associations) with strong traditions in pain research and development, 23 are internationally renowned academic and clinical institutions, 5 are specialist SMEs with cutting-edge technologies, 3 are patient organizations and 3 are professional pain/anesthesia societies.

Heidelberg University	DE
Actual Analytics LTD	UK
University of Aalborg	DK
Aarhus University	DK
Boston Children's Hospital	US
Christian-Albrechts-University Kiel	DE
ConsulTech GmbH	DE
European Pain Federation	BE
Endometriosis.org LTD	UK
European Society of Anaesthesiology	BE
European Society of Regional Anesthesia and Pain Therapy	CH
Public Assistance Hospital of Paris	FR
Hospital District of Helsinki and Uusimaa	FI
Institute of Molecular and Cell Biology in Porto	PT
Foundation for the Research of the Hospital Clínico Universitario of Valencia	SP
National Institute of Health and Medical Research	FR
International Painful Bladder Foundation	NL
King's College London	UK
MRC Systems GmbH	DE
Michigan State University	US
Neuroscience Technologies SLP	ES
Pelvic Pain Support Network	UK
PROMPTLY - Software Solutions for Health Measures	PT
Queen Mary's University London	UK
Region Hovedstaden	DK
Sapienza University Rome	IT
University of Cork	IR
Cliniques Universitaires St. Luc	BE
University of Edinburgh	UK
Jena University Hospital	DE
University of Louvain	BE
University of Navarra	ES
University of Oxford	UK
University of Münster	DE
Grünenthal GmbH	DE
Bayer AG	DE
Eli Lilly and Company LTD	UK
Esteve Pharmaceuticals SA	ES
Novartis Pharma AG	CH
Teva Pharmaceutical Industries LTD	IL

Coordinator (academia): Rolf-Detlef Treede, University of Heidelberg
Project lead (Efpia): Petra Bloms-Funke, Grünenthal GmbH
info@imi-paincare.eu
WWW.IMI-PAINCARE.EU