



PREPARE NEWSLETTER

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PREPARE's third Annual Meeting will take place on April 20th-21st 2016 in Madrid, Spain

Editorial

Herman Goossens, PREPARE Coordinator, University Hospital and University of Antwerp

Looking forward to 2016, the most important year of the PREPARE project.

PREPARE is entering a critical phase: the commencement of the observational clinical trials of WP3 (MERMAIDS-ARI, MERMAIDS-PED and MERMAIDS-ARBO; see p. 2), the adaptive trial in primary care of WP4 (ALIC4E; see p. 3) and the adaptive trial in Intensive Care Units of WP5 (AD-SCAP; see p. 2). The trials will commence during the next 2015-2016 winter season, except the Arbovirus study which will start in April 2016. The protocols and related documents will be available on the PREPARE Virtual Learning Centre (<http://prepare.ersnet.org/home.aspx>) and through the PREPARE website (<http://www.prepare-europe.eu>).

The PREPARE Consortium worked very hard to develop the clinical protocols, eCRFs, laboratory manuals, and to select the sites, but the sting was in the tail: setting up the contracts with the sites, in accordance with the EC administrative and financial rules, turned out to be the main hurdle. We realised, more than ever before, that ethical, administrative, regulatory, logistical and financial obstacles need to be solved now if we want to revolutionise the clinical research response to epidemics in Europe. The PREPARE partners participated in several of the consultation meetings on the lessons learned from the Ebola outbreak, organised by the European Commission (Luxembourg, 12-14 October) and WHO (Geneva, 1-2 December; Venice, 3-4 December). From this analysis we learned, once again, that trials happened too late mainly because of bureaucratic and logistical barriers. We also need a well-trained network of clinicians and microbiologists. For that matter, we have continued to develop the hospital care network through the New Drugs for Bad Bugs (ND4BB) project funded by the Innovative Medicine Initiative (Kostyanov et al, *J Antimicrob Chemother and Lancet Infect Dis*, November 2015). The primary care network, established during the GRACE project, was consolidated and expanded to more countries. Our final goal is to develop a network of front-line clinicians in primary care and hospital care, technically supported by a microbiology network to early detect the pathogens and IT tools to collect the data and provide real-time analysis. As soon as the clinical trials are up and running, we will focus on establishing a sustainable infrastructure for clinical research of epidemic infectious diseases in Europe. It is unlikely that the next pandemic will occur during the lifetime of PREPARE (February 2014 – January 2019); therefore, this project should evolve towards an infrastructure of ongoing clinical research on infectious diseases. We will certainly spend a great deal of time in 2016 developing a Preparedness and Sustainability Plan. For that matter, we will need to formally link with public health and regulatory authorities in Europe, and that will be another objective for 2016. We hope that our vision of a sustainable infrastructure for pandemic planning will become a tangible reality in 2016.

Regarding infectious disease outbreaks, one of the most worrying recent events is the emergence of congenital microcephaly a few months after the introduction of Zika virus infection in Brazil. Although the PREPARE Consortium concluded that the risk of transmission in Europe is extremely low, we will in anticipation adapt the Arbovirus study clinical protocol and CRF with the addition of pregnancy and neonatal modules.

Finally, PREPARE is spreading globally and Steve Webb has been allocated funding in Australia to contribute to the AD-SCAP trial.

On behalf of the PREPARE partners I would like to wish all our colleagues and friends every success in 2016.



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PREPARE CLINICAL TRIALS

A PROGRESS REPORT FROM WP3

Louise Sigfrid, University of Oxford

The Multi-centre European study of MAJOR Infectious Disease Syndromes (MERMAIDS) comprises three observational studies: acute respiratory infections (ARI) in adults (MERMAIDS-ARI), sepsis-like syndrome in infants and ARI in children (MERMAIDS-PED) and Arbovirus compatible febrile illnesses in adults (MERMAIDS-ARBO). The studies will be carried out across Europe from 2015 until 2018. The studies are a collaborative effort involving PREPARE teams based in the UK, the Netherlands, Belgium and Germany in partnership with WP6, WP7 and WP8. The teams have finalised the study protocols and ethics have been approved in the UK for two of the studies. The WP3 team has worked closely with COMBACTE and the Primary care networks for the adult studies and with PENTA and SERGAS for the paediatric study, to successfully recruit collaborating sites across Europe. We have also worked closely with the WP8 team in the design of the eCRFs.

MERMAIDS-ARI aims to recruit 2,000 adults presenting with ARI in primary care or admitted to hospital in eight countries and will be rolled out from November 2015. The objectives of the study are to identify host and pathogen-related determinants of severity of community acquired ARI in adults. Moreover, to describe the aetiology, management and outcomes of patients with ARI and to develop validated prognostic and diagnostic algorithms from host gene expression profiles (classifier genes), pathogen profiles, demographics, co-morbidities, risk factors, and clinical parameters. Our goal is to gain understanding into pathophysiological mechanisms contributing towards development of severe disease by conducting systems



medicine analysis of pathogen and patient characteristics. MERMAIDS-PED will recruit 1,000 children admitted to hospital with an episode of community-acquired sepsis-like syndrome (SLS) or ARI and age-matched afebrile controls. The objectives are

to estimate the proportion of children under 6 months of age with SLS, which is attributable to Enterovirus or Human Parechovirus infection and proportions of cases of ARI in children up to five years of age that are attributable to respiratory syncytial virus, influenza virus, human rhinovirus infection or *S. pneumoniae*. The study will commence in January 2016 in up to 13 countries.

MERMAIDS-ARBO aims to recruit up to 1,500 adults admitted to hospital with arbovirus compatible febrile illnesses in six countries in South East Europe. The study is focused on West Nile virus, tick-borne encephalitis, Toscana virus and Crimean-Congo Haemorrhagic fever viruses and designed to capture the symptoms commonly described in (re-) emerging infectious disease outbreaks as first symptoms on clinical presentation. The syndromes included are: CNS infections; haemorrhagic symptoms; undifferentiated fever and myalgia/arthritis. The study is seasonal and will commence in April 2016.

The WP3 team is also organising an Arbovirus workshop in Greece in March 2016 aimed at physicians, nurses and laboratory staff with the aim to raise awareness of early identification, diagnostics, management, surveillance and European outbreak control to strengthen surveillance and increase preparedness to (re-) emerging arbovirus infectious disease outbreaks. The workshop is organised in collaboration with WP7, WP9 and ESCMID. WP3 are also holding a PREPARE symposium at the ECCMID congress in Amsterdam in April 2016.

WP5 STUDY PROTOCOL FINALIZED

Marc Bonten, PREPARE WP5 lead, University Medical Centre Utrecht

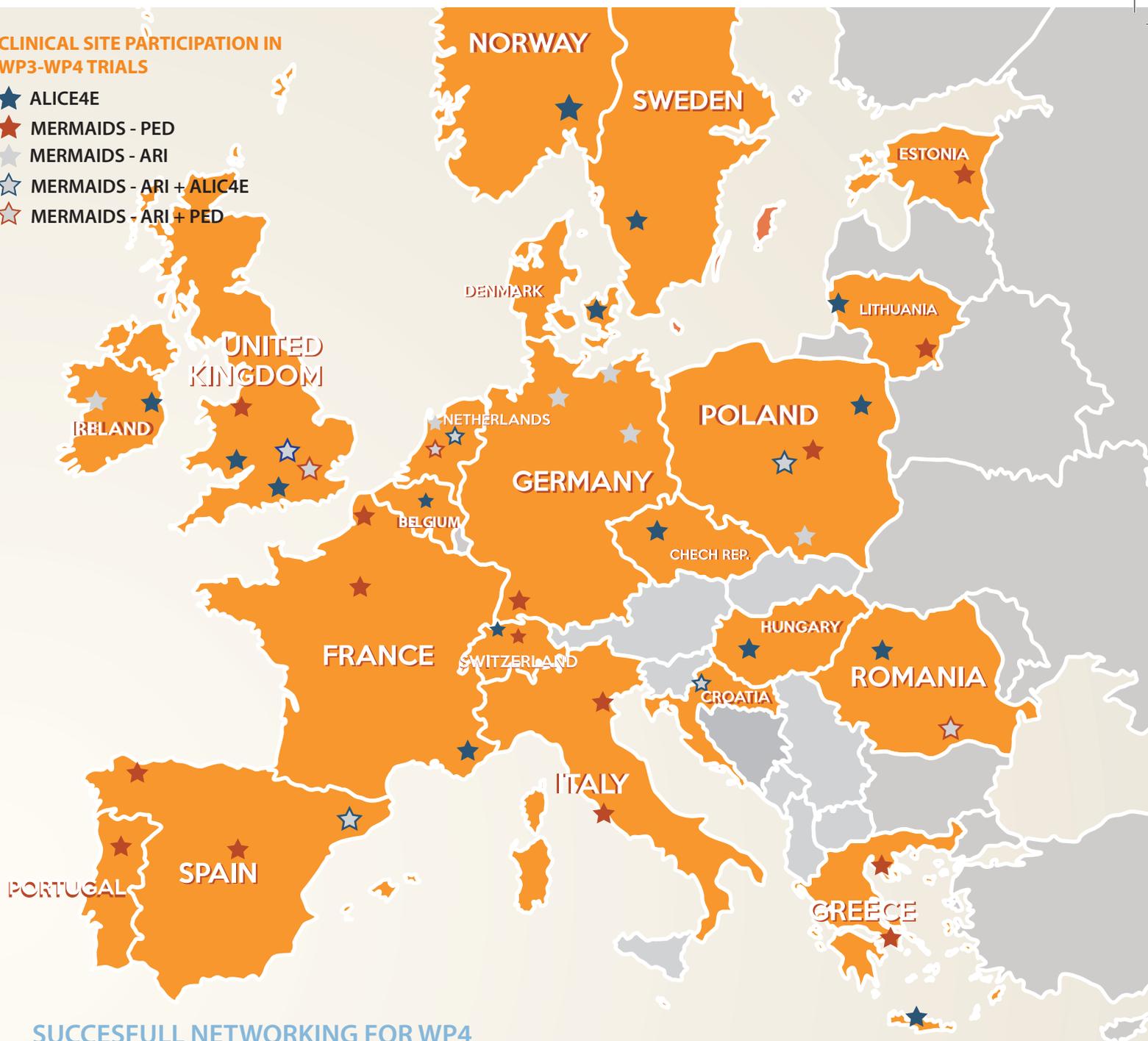
The Work package on intervention studies in Intensive Care Units - PRACTICE C (WP5) aims to evaluate different treatment options for patients with community acquired pneumonia (CAP), who are admitted to the ICU.

In the past months, the WP5 team has finalized the full study protocol introducing the REMAP design, which stands for Randomized Embedded Multifactorial Adaptive Platform. The study name is AD-SCAP: Adaptive Design platform for Severe CAP, and includes interventions from 3 treatment domains (antibiotics, steroids and ventilator strategy) that will be tested simultaneously.

The AD-SCAP study has now been approved by the Ethics Committee and the Competent Authority in the Netherlands, and the first patients were included in the feasibility study preceding the AD-SCAP study. The team is still on schedule to start the AD-SCAP study in December 2015 in Utrecht. Currently, the site identification process has yielded more than 160 sites interested to participate, with an intended number of participating sites of around 100.

CLINICAL SITE PARTICIPATION IN WP3-WP4 TRIALS

- ★ ALICE4E
- ★ MERMAIDS - PED
- ★ MERMAIDS - ARI
- ★ MERMAIDS - ARI + ALIC4E
- ★ MERMAIDS - ARI + PED



SUCCESSFUL NETWORKING FOR WP4

Johanna Cook, University of Oxford

The last few months there has been a buzz of activity in the WP4 team. Alike and Johanna have been flying around Europe training all 19 networks who are taking part in the ALIC4E Trial, from Greece to Norway and Spain to Lithuania, all corners of Europe have been covered. It has been an exciting time, meeting with partners from the GRACE collaboration and rekindling friendships, to building new links with the eight new countries that have joined the team.

One of many highlights was travelling to Klaipeda, Lithuania where the welcome was incredibly warm, and the training was followed by a visit to the beach and dipping our toes in the Balkan sea; a truly wonderful experience. The networks are fully engaged with the

study, asking really great questions, and constantly bringing fresh perspectives to the project. We are also very excited to be working with the Scandinavian teams who, in addition to addressing the main study question, will also assess the usefulness of CRP testing for influenza-like illness patients in their area. All networks have now submitted their applications to their ethical boards, with 12 out of 19 having received ethics approval. Contracts are already in place for over half of the networks, and many local recruiting sites are fully trained and ready to begin recruitment. Many useful lessons about European wide research are being learnt, for example, about insurance requirements, medication handling and the differences between ethical boards in their views about recruitment

of children and pregnant women, to mention just a few differences.

We have been working closely with our other partners in PREPARE and are well on our way to having all swabbing materials at the networks, all in pre-prepared packs to make recruitment as streamline as possible. The data management team have been hard at work developing the WP4 Research Online platform, which is almost 'battle ready'. It has been fantastic to work as a team: we have been able to incorporate many suggestions from the networks in order to ensure that the platform runs as efficiently as possible. With medication set to arrive at the beginning on November, WP4 is set fair to begin recruitment this winter!



PREPARE @ ERS

EUROPEAN RESPIRATORY SOCIETY CONGRESS 2015 IN AMSTERDAM

Anita Simonds, PREPARE WP9 lead, European Respiratory Society

PREPARE had a successful European Respiratory Society Congress with 2 major sessions. On September 26 our postgraduate course on 'Preparedness for emerging pathogens: challenges and needs' had a star-spangled line up of speakers.

Menno de Jong spoke on 'Emerging infections and pandemic planning', Marion Koopmans on Ebola: challenges for public health, what have we learnt?, Ab Osterhaus on 'Preventing the next influenza pandemic, and Theo Verheij covered Antiviral therapy, the evidence base and clinical trials. The latter set the scene perfectly for the ALIC4E trial. An added bonus was that the speakers were happy to go 'off piste' to discuss wide-ranging, up to the minute topics such as MERS-CoV, infection control management during the Hajj, and emergent infectious disease problems linked to refugee migration across Europe. Participants in the course included representatives from public health in Pakistan, pandemic capacity planning in the UK and Singapore, and orphan drug development from the European Medicines Agency. On September 29 we had a Prepare-sponsored Hot Topic symposium linking PREPARE educational activities with the WHO and ECDC,

attended by over 250 delegates. Prof Nikki Shindo (pictured), Co-ordinator of the Pandemic and Epidemic disease Department, WHO, discussed Global capacity and responses to pandemics, highlighting further lessons learnt from the Ebola epidemic. Prof Pasi Pasinen, Senior Expert for Epidemic Intelligence and acting Head of Influenza and other respiratory virus programs at ECDC, presented Translational medicine lessons from H1N1. Prof Sarah Gilbert from Oxford described the fascinating story of the fast stream development of the Ebola vaccines and initial trials, and Dr Randall N Hyer, Former WHO Civil Military Liaison Officer and co-author of the WHO Handbook 'Effective media

communication during Public Health Emergencies', showed the audience spell-binding examples of how to communicate well, and importantly, what not to do, in his session on Behaviour change and communication in pandemics: key elements of breaking bad news.

All power point presentations from all the sessions are available on the PREPARE Virtual Learning Centre <http://prepare.ersnet.org/home.aspx>, and the postgraduate course session will also appear as a video series. Together with Amy Farr and Pascal Kurosinski of the ERS we created a short highlights video as a rapid digest.



PREPARE NEWS

Third PREPARE annual meeting

The 3d PREPARE annual meeting will take place on 20–21 April 2016 in Madrid, Spain. In the last year an enormous progress has been made. Therefore we are looking forward to meet with our colleagues and discuss results and further steps.

Ebola medals for Oxford Research Team

On the 17th of September 2015, ISARIC and PREPARE WP3 leader Peter Horby brought together the collective knowledge of the team who implemented two clinical trials of experimental therapeutics under the Rapide platform during the recent West Africa Ebola epidemic. Thirty scientists were awarded the Ebola Medal for Service in West Africa. The ceremony, covered by itv News, was part of a workshop that reunited the volunteers to discuss the lessons they had learned from the trials. Read the full article on our website: <http://www.prepare-europe.eu/News/News-items/ID/37/Ebola-medals-for-Oxford-Research-Team>

EU research project guide

The European Respiratory Society and European Lung Foundation developed an EU Research project guide to promote EU funded respiratory projects including PREPARE within EU and within patient groups. Download this guide on our website: <http://www.prepare-europe.eu/News/News-items/ID/34/EU-research-project-guide>

Recommendations by Chris Butler (ALIC4E) regarding the use of antivirals during a pandemic

Together with the Wellcome Trust, PREPARE WP4 leader Chris Butler and his team reviewed all recent evidence on the use of Tamiflu during a flu pandemic.

Read his recommendations on the use of antivirals on the BBC website: <http://www.bbc.com/news/health-34466479>

Best public health poster for PREPARE

Chelsea Perfect, a US medical student who worked with the PREPARE team at Oxford, University last summer on PREPARE WP2 was awarded best public health poster presentation 2015 at University of North Carolina, Chapel Hill Medical School, US for her work entitled:

Preparing for (re-) emerging infectious disease outbreaks: A review of European clinical management guidelines for acute, community acquired CNS infections.

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Look for more information about PREPARE's projects on our website or the different social media platforms.



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In Memoriam of Janko Kersnik



To our shock and deepest regret, our dear colleague Janko Kersnik passed away suddenly on May 2015. As the representative of WONCA, Janko played an essential role in our first year of PREPARE and was particularly committed to the important development of our educational work package. We have lost a good friend and valued colleague who we will miss tremendously. On behalf of PREPARE, we are wishing Janko's family and friends all the strength to cope with this devastating loss.

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CLINICAL NETWORKS

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|---|---|--|---|
|  <p>GRACE - Genomics to combat resistance against antibiotics in community acquired LRTI in Europe</p> |  <p>TRACE - Translational Research on Antimicrobial resistance and Community-acquired infections in Europe</p> |  <p>COMBACTE - Combatting Bacterial Resistance in Europe</p> |  <p>Fondazione PENTA Padova, Italy</p> |
|  <p>CAPNETZ Stiftung Hannover, Germany</p> |  <p>European Society of Intensive Care Medicine Brussels, Belgium <i>The Intensive Connection</i></p> |  <p>SERVIZO GALEGO de SAUDE SERGAS - Hospital Clinico Universitario de Santiago Pediatrics Department Santiago de Compostela, Spain</p> | |



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