PREPARE NEWSLETTER

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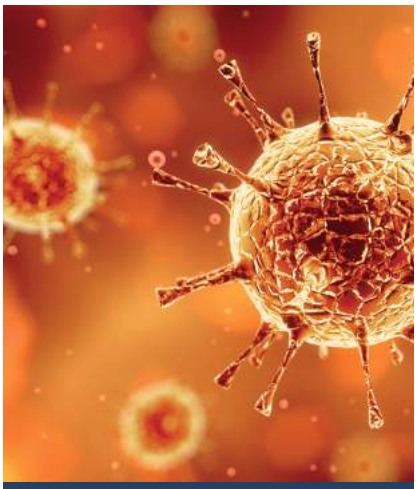
PREPARE's fourth annual meeting will take place from May 4th - 5th, 2017 in Lisbon - Portugal



In this issue

Editorial

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

The PREPARE trials were successfully launched in 2016. In 2017, we will focus on designing a European Clinical Research Alliance on Infectious Diseases (ECRAID), on developing an operational clinical research outbreak plan and on collaboration with other preparedness networks in the world.

The past year has been very challenging for PREPARE with the commencement of the three observational (MERMAIDS-ARI, MERMAIDS-PED and MERMAIDS-ARBO), and two adaptive (ALIC^{4}E; REMAP-CAP) clinical trials. We managed to overcome the many hurdles of setting up clinical trials and build an excellent relationship with the sites recruiting patients for the PREPARE trials. Therefore, I would like to express my deepest respect and gratefulness to the hundreds of clinicians, microbiologists and other healthcare providers who are working very hard to make these trials successful.

PREPARE funding is coming to an end in 2019, but we need to start thinking NOW of how we can turn PREPARE into a sustainable infrastructure for clinical research of epidemic infectious diseases in Europe. Our vision of a sustainable infrastructure became a tangible reality in 2016 as we developed a High-Level Strategy Plan for a European Clinical Research Alliance on Infectious Diseases (ECRAID)(see p. 6).

Another ground-breaking activity of PREPARE in 2017 is the development and testing of a clinical preparedness plan. This is a unique, unprecedented, ambitious and exciting initiative. To develop an operational plan of moving the PREPARE Consortium's activities from "Interepidemic Mode" to "Outbreak Clinical Research Response Mode", a collaboration will be set up with Public Health England (PHE). This outbreak response operational plan will be tested and iterated in one or more desktop exercises in 2017. The outcome of this PREPARE-PHE collaboration will be a general model for the management of the response phase and an operational clinical research response plan.

Finally, I hope that next year we will be able to establish strong links with other clinical trial networks and initiatives funded by the European Commission, such as the Latin American Zika Preparedness Network and the African EDCTP network. In November 2016, Line Matthiessen and I chaired a panel discussion on global clinical trial networks and preparedness in Sao Paulo, Brazil, and we agreed on concrete avenues of collaboration.

With ECRAID, a clinical preparedness plan and global collaboration between clinical trial networks, 2017 will be a busy but exciting year. On behalf of the PREPARE partners I would like to wish all our colleagues and friends every success in 2017.

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WP1 EARL PROGRESS

WHERE DO WE STAND TODAY?

The WP1 team

The EARL team have made great progress against the WP objective of identifying and implementing solutions to key structural ethical, administrative, regulatory and logistical (EARL) bottlenecks as well as behavioural and cultural (BC) barriers to the rapid implementation of large multi-site clinical studies in Europe in response to severe ID outbreaks. Following the first EARL report and publication of the systematic review that scoped key EARL barriers and identified potential solutions, (http://www.prepare-europe.eu/Library/Publications/ID/47) the team have:

- Analysed the data from their tracking tool that capture real-time delays arising from ethics, research and development reviews, contracting and IMP approvals progress for the PREPARE clinical studies. The final part of this work, which involves interviewing key stakeholders to augment findings from the data-tracking tool, is now well underway;

- Completed public consultation and engagement regarding attitudes to pandemic research participation through focus groups and interviews with members of the public in four European countries (Belgium, Poland, Spain, UK) (manuscript in preparation). Building on this, our work is progressing well on a European Public engagement survey (approx. 5,000 participants) to determine acceptability of adapted recruitment processes, and use of routinely collected data and clinical samples for pandemic research;

- Conducted a break-out session and interviews at the European Society of Paediatric Infectious Disease (ESPID meeting), 2015 (report submitted for PREPARE) and a follow-on on-line expert consensus study to identify the key priorities for conducting paediatric pandemic research regarding the priority needs of paediatric clinicians and researchers to conduct pandemic research. (Analysis and manuscript in preparation);

- Conducted a Year 1 Process Evaluation of the ALIC^{4}E study, which involved interviewing recruiters and patients (adults and parents) from a number of sites about their experiences of taking part in the study. We also elicited recruiter and participant views on alternative processes to make research more feasible during a pandemic (alternative consent and trial design). Constructive feedback on the ALIC^{4}E processes has been delivered to the ALIC^{4}E study team who have implemented real changes based on this to optimise study processes and improve efficiency;

- Developed a strategy to identify the additional barriers and propose potential solutions on the issue of 'contacts'. This was highlighted as a major barrier by PREPARE collaborators at the PREPARE Annual meeting in Madrid. We are currently interviewing key stakeholders including study coordinators, PI's and persons in University legal departments, and finalising a complementary data collection tool;

- We are collaborating with Anita Simmonds, WP9, to develop educational materials that might allow us to disseminate this work;

- An updated EARL report has now been disseminated to the WP leads prior to PREPARE wide distribution will be available soon and an 'EARL Solutions' report will be available next Spring. Finally, EARL are developing a pandemic outbreak plan that will allow us to capture real time experiences during a future pandemic that will contribute to debates about ethical conduct of studies during this time.

PREPARE Arbovirus workshop 29 - 31 March 2017

The aim of the workshop is to improve the participants' knowledge of identification and management of arbovirus infections and outbreaks at local and European level, with the aim to strengthen preparedness to (re-) emerging arbovirus infections across Europe. Course topics will include a review of arboviruses of clinical importance to Europe, including, symptomatology and differential diagnostics. Moreover, an overview of European organisations involved in surveillance, control and outbreak response will be presented. The course will be delivered by European experts through a dynamic mix of lectures and interactive sessions including a European outbreak response exercise. There is an opportunity to apply for grants which covers all costs except travel.

For more information, to register and apply for grants: https://escmid.pulselinks.com/event/13434

WP3 MERMAIDS SEASON 2

The WP3 team

MERMAIDS-ARI

The MERMAIDS-ARI study has got off to a good start in season two, with patients recruited from primary and secondary care sites within the first week of the season, which started on 1st October 2016. There are currently 22 sites open to recruitment across seven countries: Croatia, Germany, Ireland, Poland, Romania, the Netherlands and the United Kingdom, with additional sites expected to open shortly. To help reach the recruitment targets we have added additional secondary care sites in each country for season two, taking the total number of sites to 30 (8 primary care, 22 secondary care) across eight countries.

The Antwerp team has analysed the samples from the patients recruited during season one, and the results informed the interim analysis report produced by the statisticians in Oxford in time for the Annual Steering Committee meeting which took place in September.

Despite a delayed start to recruitment in season one, the five sites that opened enrolled 91 patients. The reference laboratory diagnostics showed that 27% of patients tested positive for Influenza, 8% for Infl. B, and 19% for Infl. A. 12% of patients tested positive for Rhinovirus, 7% for Coronavirus, and 2% for RSV. Despite the small sample size, the data showed that a good proportion of patients tested positive for ARI pathogens and the rates of comorbidities amongst the enrolled patients were in line with the estimates used for the sample size calculations. The team at AMC are currently selecting samples for microarray analysis.

MERMAIDS-ARBO

The MERMAIDS-ARBO study has been open to recruitment over the summer season with 162 patients recruited into the study from secondary care sites in Albania, Kosovo, Romania, Bosnia-Herzegovina, Greece and Croatia. The recruitment period for season one ended on the 31st October 2016. The patient samples collected will be batched and shipped to Antwerp after completion of all follow up visits. The central laboratory analysis is scheduled to take place over winter and spring by the teams at Antwerp University, Erasmus MC and University of Bonn. The WP3 team look forward to reporting on this next year.

A 3-day interactive Arbovirus workshop aimed at clinicians and laboratory staff in southeast Europe organised in collaboration with WP9 and ESCMID, will be held in Zagreb, Croatia from 29 – 31 March 2017.

PED-MERMAIDS

The PED-MERMAIDS study, sponsored by the PENTA foundation has made good progress over the last few months, and is now open to recruitment in 4 sites. The WP3 team at St. George's University Hospital in London, in collaboration with PENTA have already issued 6 'green light letters' to sites with a further 6 to be issued shortly. This means by January it is likely that over 70% of the PED-MERMAIDS sites will be open for recruitment, with the rest expected to follow imminently. Of all 17 sites, 16 have contracts in place with 12 sites granted ethical approval. Of the remaining sites without either ethical approval or contracts in place, in the majority of cases, submissions have been made and the WP3 team are awaiting the outcome.

In addition, the team in Antwerp are making sure all sites are provided with sample kits, and in Utrecht, Research Online (eCRF) is now live for PED-MERMAIDS. The monthly Trial Management Group and Trial Steering Committee telephone conferences are well underway. Monthly PED-MERMAIDS newsletters are now being sent out.

Everyone in the PED-MERMAIDS team is working extremely hard to make sure that by early 2017 all of the 17 sites across 11 countries are recruiting.

LAUNCH SECOND ALIC^{4}E SEASON

The WP4 ALIC^{4}E team

The ALIC^{4}E Trial got off to an amazing start last winter with 492 participants recruited from 16 networks across Europe! Two networks recruited over 80 participants, and another two networks recruited over 50!! We are so delighted with the effort that everyone has put in to making this happen. It has been very challenging to ensure all the approvals, contracts, and insurance are in place, but the success of our first pilot season is a testament to the hard work, commitment, personal sacrifice and creative energy of all the teams. We know that many of you have gone way beyond the extra kilometre for ALIC^{4}E.

During the summer, we have been working together to update the protocol, clean all the data, and learn from each other's experiences to increase recruitment and follow up during the coming winter. Everyone really enjoyed meeting together in Madrid to learn about how the whole of PREPARE is going, to see exciting data beginning to emerge from the trial swabs, and to hear how the whole ALIC^{4}E team is doing. There were many helpful hints about how make contact with participants, and strategies for improving recruitment that were shared between all the networks. We have thoroughly enjoyed catching up with old friends, making new ones, and contributing to a landmark study in applied primary care clinical and biological sciences in this amazing collaboration!

The weather is finally turning colder and the next flu season is now upon us, with the Netherlands and Ireland open now to recruitment and more networks to follow soon. We have been making sure that everyone is up to speed with all that needs to be done and that they have the supplies needed to ensure good recruitment. All the networks are busily re-training sites, setting up new sites, making the necessary amendments to local systems to make sure we are running an efficient trial. We have increased the per-patient payment to the networks for this next season to support participant follow up. Networks are either using this to directly thank the participants with a 'thank you' gift, or to add to the capacity of the team to follow up the participants. We are very much looking forward to this next recruiting season really getting underway!

We thank the entire ALIC^{4}E Family for all your amazing contributions!! Keep an eye on when flu emerges where you are! You will hear from us when there is a green light to open recruitment for this coming season.

WP5 study going global

The WP5 team

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.

It was an eventful year. We successfully completed the feasibility study. The lessons learned from this observational study allowed us to improve the platform for the full study. Additionally, we started with the main part of our study with as highlight the first inclusion in April 2016. The inclusion of CAP patients has been slow during the summer months but is hopefully boosted when the CAP season starts in the fall. In November 2016 we finalized our new protocol and implemented a new name and logo namely REMAP-CAP
(Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia). The redesigning of the protocol into a modular protocol and the change of name to REMAP-CAP is also part of the collaboration with the Australian team. And hopefully, REMAP-CAP will also move to Canada, where a grant application has been submitted recently. At our investigator meetings in both Madrid and Milan, participants are very actively involved in the discussions and very enthusiastic about our adaptive RCT and its novel design. The REMAP-CAP study will definitely meet challenges when it continuously expands across the globe, but the REMAP-CAP Trial Steering Committee and all others involved remain very keen on making this exciting project a great success.

WP7 PREDICT

European Platform for REsearch and support on Diagnostics for Infectious disease Clinical Trials

The WP7 team

WP7 is geared towards project objective III: To establish PREDICT: the European Platform for REsearch and support on Diagnostics for Infectious disease Clinical Trials providing "State-of-the-Art" diagnostics and laboratory support for the inter-epidemic clinical studies in PRACTICE as well as those in response to future severe ID outbreaks.

The first PREPARE samples that were analysed were collected in the framework of ALIC^{4}E. In this study, participants were recruited in primary care networks across Europe last winter season during a period with high influenza incidence. Each participant had a diagnostic swab taken at baseline that was subjected to the Idylla influenza/RSV POCT (BioCartis platform) in Antwerp. An overall positivity rate of 51.2% was found. The majority of the infections were caused by influenza B (27.2%), followed by influenza A (21.9%) of which the majority was influenza A H1N1. RSV B was only detected in 2.1% of the specimens. The second study for which samples were analysed was the MERMAIDS-ARI study. Here, samples from 89 patients were analysed by a multiplex PCR (Fast-track, respi 21 plus). The overall positivity rate was 59.6%, but with large differences between the networks. Influenza A was most frequently detected (20.2%), followed by S. aureus (14.6%), rhinovirus (12.3%), influenza B (9.0%), coronaviruses (6.7%), S. pneumoniae (3.4%), RSV (2.2%), and metapneumovirus, bocavirus and M. pneumoniae (each 1.1%).
For the MERMAIDS-ARBO study analysis, 470 patient kits were prepared and distributed to 21 recruiting sites spread over Albania, Bosnia and Herzegovina, Croatia, Greece, Kosovo, and Romania. Samples collected during the first season of the study will be collected for analysis soon.

ZIKV-response

Dr. Gail Carson, ISARIC

Fernando Bozza (FIOCRUZ & BricNET), one of ISARIC's Latin American focal points, brought the rise in cases of microcephaly that were, then, potentially related to ZIKV to our attention early December 2015 during ISARIC's Stakeholders Meeting in London. Following his presentation, we convened an emergency meeting to discuss how best to support him. A number of ZIKV-response related activities were started as a result of this discussion, some of which are still ongoing.

Firstly, a website – http://www.zikainfection.org was created for clinical research use. The site offers free access to data collection tools, and aims to encourage data sharing in the near future through a core group of data variables that are presented as series Case Report Forms (CRFs). The work done to create and modify the CRFs was done in conjunction with Louise Sigfrid of PREPARE Europe, REACTing, CONCISE and a number of other experts and partners who have reviewed the documents continuously through their development.
Additionally, ISARIC's Coordinating Centre (CC) has been working with WHO Geneva and IDAMS on developing a Clinical Characterization Protocol for ZIKV, which is currently going through an internal WHO review process. We have also hosted regular teleconference calls with colleagues from Zika affected countries, including colleagues from Asia and West Africa, to discuss new findings, support researchers, help with preparedness etc. The calls currently gather more than 100 participants, and they are an example of how ISARIC can be used as a neutral platform for information exchange and knowledge transfer.

ISARIC's CC will continue to work with researchers and public health colleagues to enable an efficient ZIKV response for the foreseeable future.

ECRAID

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

European Clinical Research Alliance on Infectious Diseases (ECRAID): We have a vision!

ECRAID is a new concept that should revolutionize clinical trials in infectious diseases in Europe and even beyond. It is the result of the commitment of the European consortia COMBACTE (www.combacte.com) and PREPARE to deliver on their common objectives to establish sustainable high-functioning broadly inclusive EU clinical trial and laboratory networks, for antimicrobial resistance and pandemic threats. However, ECRAID's ambition is much larger as it would perform a broad array of diagnostic, therapeutic and preventive clinical studies on antibacterials, antifungals, antivirals, anti-parasitic drugs and vaccines, both interventional and non-interventional. ECRAID would run "warm-base" studies, continuously enrolling patients, as well as "fit-for-purpose" studies designed specifically to study new diagnostic, treatment and prevention strategies. ECRAID should provide a robust infrastructure capable to efficiently perform the full spectrum of clinical trial activities: from study design, to execution, to reporting. These activities are coordinated by a lean, centralized organization as a single point of access for all relevant stakeholders.

A High-Level Strategic Plan was delivered in November 2016 by a group of key partners of PREPARE and COMBACTE, led by Marc Bonten (coordinator COMBACTE and PREPARE - WP 5) and myself. In 2017, a public-private partnership should develop a detailed Design Plan.

PREPARE @ ERS 2016

Anita Simonds, WP9 lead

PREPARE Educational highlights at the European Respiratory Society Congress, London September 2016

PREPARE in conjunction with ECDC held a Postgraduate course 'Infection control in epidemics: the evidence base for healthcare workers' at the European Respiratory Society congress this year at the Excel Congress Centre, London.

During the keynote course Pieter Fraaij discussed the important topic of protecting healthcare workers in epidemics using the experience from MERS and Ebola, and Thomas Mollet from ECDC extensively covered the role of epidemic intelligence and surveillance in predicting and managing epidemics, including innovative use of social media.
Laura Fregonese of the European Medicines Agency discussed important new and evolving thoughts on Fast track trials for drug and vaccine development.
There was a lively interactive debate with delegates attending from as far and wide as Slovakia, Silesia, Nigeria, St Petersberg, Guanzhou, China, London and Ireland - a number of these colleagues being in charge of pandemic planning for their country. The session was chaired by Pasi Penttinen of ECDC and Anita Simonds of PREPARE/ ERS. All presentations (in video and power point format) and background information from the course will shortly appear on the PREPARE Virtual Learning Centre accessed via the link on the PREPARE homepage.

Later in the congress programme, in an ESWI-supported translational medicine symposium on 'Influenza and respiratory physicians', Albert Osterhaus described trends and fears regarding the epidemiology of flu over the last decade, and Janet McElhany and Marco Restrepo covered the protection of high risk patients from flu, and the lessons learned in the management of critically ill influenza patients, respectively. Finally Peter Openshaw from PREPARE presented 'Who get influenza and why?' to a maximum capacity audience of over 400 delegates. Also these presentations will be available via a weblink from the Virtual Learning Centre.

Pieter Fraaij

PREPARE NEWS

PREPARE fourth Annual Meeting

The fourth general assembly of the PREPARE consortium will be held from May 4th - 5th 2017 in hotel Sana Lisboa, Lisbon, Portugal. Registration will open soon!

New PREPARE members

James Lee joined the Oxford team in July 2016 to take over the day-to-day responsibility for managing PREPARE WP3 projects. James has experience in research governance, clinical trial monitoring and a background in biological sciences and exercise instruction.

Frank van Someren Gréve joined the AMC team in 2016 to support coordination and execution of the Mermaids-ARI study in the Netherlands. Frank is a physician with a dual affiliation at the AMC Departments of Intensive Care and Medical Microbiology. He recently coordinated a Dutch multicenter study on the role of respiratory viruses in mechanically ventilated ICU patients, forming the basis of his current PhD research.

Connect

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

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CLINICAL NETWORKS

GRACE - Genomics to combat resistance against antibiotics in community acquired LRTI in Europe

TRACE - Translational Research on Antimicrobial resistance and Community-acquired infections in Europe

COMBACTE - Combatting Bacterial Resistance in Europe

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