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Newsletter for the International Severe Acute Respiratory and  
Emerging Infection Consortium

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# ISARIC News

Issue 1 | Q1&2 | 2013

## Jeremy's message

Welcome to the Q1&2/2013 ISARIC Newsletter. I am very sorry for the lack of a Q1/2013 Newsletter, events somewhat overtook us! But we hope you will find this update interesting and useful.

The last year with the emergence of H7N9 and NCoV might seem extra-ordinary, two potentially major emerging infectious disease threats occurring simultaneously in different parts of the world. But the reality is that with the much better surveillance now in place in many parts of the world we are inevitably going to identify such novel (or re-emerging) threats on a much more regular basis.

In addition to the emergence of these high profile zoonotic pathogens there have also been regional outbreaks of Hand Foot and Mouth Disease in Asia, Dengue in new areas of the world, Chikungunya, Crimean-Congo haemorrhagic fever, Hepatitis E and many more plus the continued emergence and spread of perhaps the greatest emerging infectious disease problem of all, antimicrobial drug resistance.

With better surveillance has come better sharing of information and samples, perhaps not perfect yet and there is much work to be done, but certainly better than a decade ago. Although there have been great



## Updates

- ✓ ISARIC part of [PREPARE](#) (EC FP7)
- ✓ WHO/ISARIC [SARI BSP and database](#) in use
- ✓ PHE/ISARIC [Decision support tool](#) (nCoV)
- ✓ Work on Convalescent plasma protocol
- ✓ 70 members and counting - 6 networks have joined in the last 6 months
- ✓ GHT project funded (Kath Maitland, KEMRI-WT & Kathy Rowan, ICNARC)
- ✓ Jeremy Farrar to become the [Director of the WT](#)
- ✓ Li Ka Shing award to ISARIC

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- clinical calls held
- ✓ Ken Baillie and Jake Dunning seconded to WHO
  - ✓ Antiviral Combinations for Avian A(H7N9) and Other Influenza Infections: Dunning, Baillie and Hayden Submitted to Lancet Infectious Diseases
  - ✓ Discussions with Wellcome Trust, BMGF, MRC, INSERM and LKS Foundation about future of ISARIC.
  - ✓ Institut Pasteur funds for E-learning project
  - ✓ ISARIC-baby Isaac 'Zak' Carson born, 3 June, Congratulations Gail!
  - ✓ [WHO and KSA joint mission](#), KSA, 4-9 June
  - ✓ WHO Scientific Meeting on MERS-CoV, Egypt, 18-19 June
  - ✓ Singapore Roundtable: networking in South-East Asia, 14 July
  - ✓ H7N9 conference and workshop, China, 14-17 August
  - ✓ WHO/ISARIC Mission to Tunisia, 27-29 August
  - ✓ Joint KSA and WHO Mass Gathering Meeting, Riyadh, 21-23 September
  - ✓ EC F2F Meeting, Oxford, 26-28 September



## Working Group Updates

WG1: Members from working group one have continued their work on an interventional protocol on Convalescent plasma, intended to be a response to nCoV. There is also work being done on a protocol on Interferon. Another update is that Kath Maitland and Kathy

improvements in communication and sharing and much better surveillance the 'Clinical Research Response' still lags behind, we still do not know how to actively treat patients, or use therapeutic interventions to prevent secondary transmission in any of the infections I mention above.

This was the issue that led to the initial discussions by the Heads of International Research Organisations (HIROS) and a subsequent meeting hosted at the Wellcome Trust in 2011, which led to the setting up of the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC). I believe it is even more relevant today as the response to the pandemic of 2009, and subsequent epidemics have shown.

I would like to highlight a few of the major activities that partners within ISARIC have been involved with over the last few months.

The Middle East and in China have of course borne the brunt of the outbreaks of nCoV and Influenza H7N9. ISARIC has benefited enormously by the close collaboration with colleagues in both regions and through a series of teleconferences, workshops, and meetings case management has been shared and ideas discussed. The meetings in Beijing and Shanghai and Cairo in August and in Riyadh in September have brought together people from the regions, with clinicians with prior experience from looking after patients with SARS, H5N1, H1N1, and the critically ill. Further work is planned in both China and the Middle East on clinical intervention studies to establish the best treatment for patients with both nCoV and H7N9 and in understanding pathogenesis.

Our warmest congratulations go to Professors Herman Goossens and Menno de Jong and colleagues who led a European wide consortium granted a large EU FP7 grant to support PREPARE -

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[Global Health Trials](#) bid was successful. ([See last newsletter](#))

WG2: Supported the development and PPI for the [SARI BSP and WHO Natural History Protocol](#). The group has also gone through the first round of the results of the Delphi study on Core Outcome Measures, and hope to run the second round in parallel with the EC F2F meeting in Oxford.

WG3: Completed the prioritisation and integration of [biological sampling](#) studies to create a single combined biological sampling protocol for use in severe acute respiratory infection. Together with case report forms created by others within ISARIC and WHO, this forms an versatile biological sampling protocol that is designed to adapt to the changing needs of different outbreaks, and to different resource levels.

WG4: Has undertaken a membership survey, aiming to document the achievements and research capacities of ISARIC's 40 member networks, which are undertaking clinical research in 90 countries spread over all continents. The results of the survey were presented at the [Singapore Roundtable](#) and will be submitted for publication in the near future. Other activities undertaken by WG4 include liaison with public health authorities to understand their perspectives about clinical research priorities and engagement with member networks to identify their unmet needs to enhance their research

Platform for European Preparedness Against (Re)-emerging Epidemics in response to the EU call for a consortium to provide EU wide leadership on "Clinical Research in Epidemics". This was a monumental effort superbly led Herman and Menno. PREPARE is innovative, ambitious, comprehensive, crosses boundaries and disciplines and I believe provides real leadership within the European Union and a model for all of us wherever we work in putting clinical research at the heart of the response to a public health emergency. ISARIC is intimately linked with and is a committed partner of PREPARE. We wish Herman, Menno and all colleagues in PREPARE every success with this superb programme.

The relationship between ISARIC and the World Health Organisation has gone from strength to strength. We are very grateful to the commitment and encouragement of Dr Nikki Shindo and colleagues at WHO. During the development of generic and specific protocols for H7N9 and NCoV Dr Jake Dunning and Dr Ken Baillie were seconded to WHO Geneva for short attachments to support the development of these projects. We are grateful to Imperial College and Roslin Institute Edinburgh for facilitating the attachments and for WHO for being such a welcoming host.

Finally nothing happens without the work of the Co-Ordination Centre of ISARIC led by Dr Gail Garson and Kajsa-Stina Magnusson. Both have been incredibly busy both professionally and personally with Kajsa getting married (and forgoing her honeymoon for the sake of ISARIC) and Gail giving birth to Zak in July. Without their unselfish dedication ISARIC would not exist today. Kajsa has also just been awarded a further Li Ka Shing Foundation grant for a flexible "Seed Fund" for ISARIC which can be available immediately to support the development or implementation of initial clinical research studies should a new outbreak occur anywhere in the world.

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particularly related to ethical and regulatory pre-approval of clinical research for future outbreaks will be enhanced by liaison with [PREPARE](#).

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**Would you like to join a working group?**

**Get in touch**

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## **PHE/ISARIC Decision Support Tool nCoV**

**Public Health England and ISARIC has published a Decision Support Tool that is offering support to clinicians considering options for treatment of patients diagnosed with novel coronavirus (MERS-CoV).**

Based on both published works and unpublished data shared by clinicians, researchers, and public health experts during a series of clinical calls on nCoV - the document considers and rates potential options for treatment such as Convalescent plasma, Interferon, Protease inhibitors and Intravenous immunoglobulin.

The tool, which is freely available for download on the [ISARIC](#) and [PHE](#) websites, is under constant review and includes findings and data found through an extensive monthly literature review performed by the

We are very grateful to the support we have had from the Wellcome Trust, Bill and Melinda Gates Foundation, the Medical Research Council UK, Singapore Ministry of Health, INSERM France and the Li Ka Shing Foundation. It is only with such support can ISARIC continue to grow in the future and help ensure that clinical research is part of the response to any epidemic.

Finally as many of you will know I will be changing my role from the 1<sup>st</sup> October 2013. It has been a privilege to be involved with ISARIC over the last two years. ISARIC was at its inception and I believe remains today ahead of its time. The challenge is having developed this concept how to now make such a paradigm shift happen in how we prepare for and respond to a public health emergency. It is absolutely crucial that clinical research is at the centre of the public health response to any emerging health threat. It is simply unacceptable that we do not have the evidence on which to develop policy, practice and guidelines for the treatment of patients with novel influenzas, nCoVirus, hand foot and mouth disease, hepatitis E, Chikungunya, viral haemorrhagic fevers and so many more emerging infections.

The massive expansion in global surveillance will only be worthwhile if we learn how to look after patients and communities who we identify to be suffering from an emerging infection or by the spread of drug resistance. Surveillance and traditional public health responses need an effector arm and in the early days and months of an epidemic that will largely be by knowing how to effectively treat a patient with the infection.

There are a huge number of regulatory, ethical, logistics, practical barriers to the conduct of any clinical research nowadays and these are particularly acute during an epidemic. But ISARIC needs to

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collaboration with Oxford's Bodleian Library.

The literature review will be adapted and made available on the ISARIC website shortly.

## Singapore Roundtable

**A networking event for ISARIC members and interested networks in South-East Asia took place in Singapore in July. Sponsored by Singapore Ministry of Health, the event gathered 48 participants representing 20 networks and 16 countries in the region and beyond.**

Though primarily an opportunity to get to know other networks in the region, the event, hosted at the National University of Singapore and arranged by the Singapore Infectious Diseases Initiative, offered an opportunity to present the SARI BSP, and to introduce ISARIC. Both generated interest among the networks present, which is promising for ISARIC's further activities in the region.

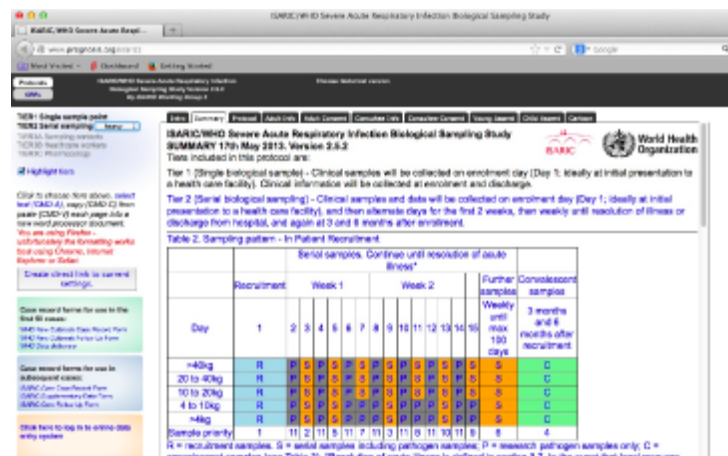
A Regional Hub is currently being set up at OUCRU Vietnam, and though it is not likely to be the only regional hub in Asia, it is a first step towards a sustainable global roll-out of ISARIC.

**E-learning @ isaric.org**

address these issues and persuade an often skeptical research community, the public and the medical and public health communities of the critical importance of clinical research during the early stages of an epidemic.

The European Union has shown real leadership by supporting the PREPARE Consortium. I hope that through ISARIC others will follow in the future. I will continue to follow the development and impact of ISARIC in the years to come in my new role. I wish ISARIC every success and have every confidence in ISARIC delivering on its ambitious plans.

Jeremy Farrar  
ISARIC Chair



*Pictures above: Screen shot of the protocol summary (top); Dr Do Lien Anh Ha presenting the translated protocol to clinicians in Ho Chi Minh City, July 2013 (bottom, left); and screen shot of the database (bottom, right).*



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Institut Pasteur (IP) has set aside €30000 for the development of e-learning modules in Good Clinical Practice, Surveillance, and Biosafety, which will be made available on the ISARIC website.

The funding, which is part of a collaborative effort between IP, ISARIC and The Global Health Network (TGHN) will be used to employ an e-learning assistant at IP Paris, who will work closely with Liam Boggs of TGHN.

Liam has previously developed a range of e-learning modules, which are one of the most popular features of TGHN. Since it was launched in August 2011, the [E-Learning Centre](#) has had over 10,500 visits, and the modules have been taken by over 5000 users to date.

"The E-Learning Centre is so successful because of its accessibility" says Liam Boggs, "the short courses offer the 'how to' cross-cutting training needed to equip researchers with the skills to design, operate, report and govern research - without impeding bit rate. This setup works in areas of low band width internet connection" he explains.

The completion date for the project is not yet decided, but the modules will be added to ISARIC's website continuously.

## Feature article: ISARIC-WHO SARI Biological Sampling Protocol

*Kajsa-Stina Longuere, Jake Dunning, Ken Baillie and Laura Merson* - ISARIC, in collaboration with WHO, has developed and published a Biological Sampling Protocol (BSP) for Severe Acute Respiratory Infections (SARI). Designed to be generic and flexible, the protocol aims to capture all emerging SARI, including current threats such as H7N9 avian influenza and the novel coronavirus, MERS-CoV.

The SARI BSP and supporting documents are available for download [through the ISARIC website](#), and is building on previous work towards a BSP by ISARIC's Working Group 3, chaired by Ken Baillie at the Roslin Institute, in collaboration with WHO through Nikki Shindo and her team at WHO Geneva.

Having a pre-prepared, generic protocol is a key step to enabling research teams around the world to launch studies quickly in the event of an outbreak. It is vital that key biological samples are collected in a standardised manner from as many patients as possible within a typically narrow window of opportunity. Utilising the expertise of member networks, the selection of samples and the sampling frequencies have been designed by WP3 to ensure this can happen.

In addition to collecting biological samples, the collection of a core clinical data set is essential for the interpretation of any laboratory findings. Furthermore, high-quality clinical data that are made available rapidly can assist the development of clinical management guidelines and public health policies. Again, ISARIC is working with WHO to develop focused case report forms (CRFs) and associated

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## WHO and China CDC H7N9 Conference and Workshop in Beijing and Shanghai

*Peter Horby* - The recent outbreak of a novel avian influenza A/H7N9 in China, which has resulted in 135 cases and 44 deaths as of 27th August, is a reminder of the ever present threat of the emergence of new pathogens, and a validation of the need for ISARIC.

The Chinese authorities and clinicians have acted with great expertise, competence and transparency, and this is reflected in the rapid publication of a large number of articles in high impact journals.

Much however remains to be learned about this novel virus, leading the Chinese Center for Disease Control and Prevention to convene a conference in Beijing and Shanghai (August 14-16), bringing together experts and provide an update on the current situation and the latest research progress of human infections with H7N9 in China.

This was followed on August 17th by a WHO workshop on the clinical care and

documents to meet these demands. A core CRF and a more detailed CRF are already available on the [ISARIC website](#). Versions that can be completed electronically have also been developed, along with an accompanying database (see below).

“Panic and fear have ruled the initial responses to almost every emerging infectious disease outbreak. The public health and laboratory science communities have gained confidence through experience, but what about the clinical community? asks Nikki Shindo. “We have to make a step forward in clinical research that can inform patient care in epidemics, or we will just regret further missed opportunities!” she continues. Nikki Shindo emphasizes that the only solution is to have the system set up in the time between epidemics and make sure good data are collected to generate the knowledge necessary to better treat and manage patients when these events inevitably occur. In this time of mass air travel and international human movement and trade, an emerging pathogen can travel around the world in a matter of hours and can cause multiple, international outbreaks. Initial sporadic cases and clusters occur here and there, but with standardized protocols freely available, good sample sizes can be achieved much faster and patient lives can be saved and secondary transmission reduced. “Quality data give power to the study and this will enable WHO to make recommendations with greater confidence.

We consistently suffer from only having access to ‘low quality evidence’” and hence can only make weak recommendations. WHO and ISARIC are working together closely, attempting to fill this gap in the global public health landscape”

### Tiered approach

The protocol with supporting documents is currently being rolled out or being considered for implementation in more than 13 countries globally,

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infection with novel influenza viruses, at which ISARIC was represented and where the ISARIC observational protocols for Severe Acute Respiratory Syndrome (SARI) were presented and discussed. Following the workshop, the team travelled to the Shanghai Emerging and Re-emerging Infectious Diseases Institute, for further detailed discussions with Shanghai clinicians on H7N9 research.

In partnership with WHO, ISARIC members are now working with clinical colleagues in Beijing and Shanghai to adapt and implement the ISARIC observational protocol in local clinical networks in these two large cities in readiness for the potential return of H7N9, or any other SARI, in the winter.

## ISARIC visiting South East Asia

**ISARIC's Programme Manager visited South-East Asia in July, meeting with ISARIC members and potential members in Thailand, Hong Kong, Singapore and Vietnam.**

Aiming to forward ISARIC's global ambitions, the trip's main objective was to discuss collaboration with partners in the region, introduce ISARIC and the SARI BSP and to map potential challenges and interests related to the establishment of a Regional Hub in Ho Chi Minh City.

including Vietnam, UK, and Singapore. To facilitate global implementation, the BSP includes a tiered approach to sampling and data collection, which makes it adaptable to high, medium and low resource settings and sensitive to resource limitations that may occur during outbreaks. It is up to the sites and networks implementing the protocol to choose which tier they wish to implement. When the protocol is adapted to local context for submission to the Ethical Committee a single tier can be selected, or all tiers can be included in the protocol. Sites that obtain approval to implement all tiers have the flexibility of real-time adaptation as an outbreak hits or evolves to ensure that the most relevant sampling schedule is used for all patients. This approach has been used in Ho Chi Minh City, Vietnam to minimize the risks to patients while maximizing the critical scientific output.

### Sampling

As the pathogen affecting research participants may yet be unknown, the BSP includes sampling of blood, the respiratory tract, urine, stool and other infected sites. The protocol is flexible such that samples, which are not of relevance to a particular pathogen, will not be taken. The tiered approach also offers options of sampling frequencies so that only samples, which answer the most pertinent scientific questions, will be drawn. These may change throughout the course of an outbreak and can be adjusted according to availability of local resources, number of patients diagnosed regionally/internationally, severity of disease, etc. The structure of the BSP ensures that samples required for clinical care have priority over research sampling and that clinical and research sampling should coincide whenever possible.

### Data management

The BSP comes with a Core Case Record Form (CRF) and a Core Follow Up Form, all of which are available [online](#). Additional data collection modules will be added in the coming months to allow the



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VIZIONS' Dak Lak study team, Daklak Hospital, Vietnam

## Network in Focus: VIZIONS - Exploring Zoonotic Infections

**Aiming to develop baseline data on exposure risk and develop the infrastructure to study and respond to the next emerging infection in South-East Asia, VIZIONS -The Wellcome Trust Vietnamese Initiative on Zoonotic Infections - is a multifaceted project to study disease trends, the potential of zoonotic infection and emerging infectious diseases in Vietnam.**

Supported by a Wellcome Trust Strategic Award to OUCRU, Edinburgh University, The Sanger Institute and the Global Viral Forecasting Initiative (GVFI), VIZIONS is aiming to fill the animal/human disease gap by investigating viral pathogens on both sides of the species barrier.

The project, led by Professor Jeremy Farrar and Dr Stephen Baker in Vietnam, has been running for 18 months and has established a functional disease surveillance system within the Vietnamese healthcare system and a cohort study of

amalgamation of additional types of data with the clinical data where desired.

An online database is available for input of data from the CRFs. International data can be combined on a single server, or copies of the database can be hosted in regional servers for any sites that require a more regional approach to data management.

The database is built on the CliRes data management platform, produced and maintained by Hien Ho Van and his team at OUCRU, Ho Chi Minh City. "The design of the CliRes allows for rapid production of new databases - in a matter of hours a CRF can be programmed into an electronic database and ready for input" says Laura Merson, Head of Clinical Trials at OUCRU Ho Chi Minh City and an active member of the SARI BSP working group. Being web based makes it accessible globally, and its flexibility and simple design makes it very easy to use.

The database has been reviewed and piloted by investigators around the world, and ISARIC and WHO have plans to move forward with CliRes and joint initiatives on open-access software. A library of CRFs and robust data protection/ data sharing policies are in the pipeline.

### ISARIC-WHO collaboration

As an ISARIC Observer (participating non-member), the WHO is working closely with ISARIC to design and promote the BSP and other aspects related to a clinical research response to current threats nCoV and H7N9. The collaboration has resulted in two secondments, one of Ken Baillie and the other of Jake Dunning (Imperial College London/MOSAIC) to WHO Geneva. In addition to working on protocol harmonisation, they also helped set-up and run joint international clinical teleconferences, which aim to provide assistance to clinicians on the ground, facilitate sharing of clinically-relevant information,

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the higher risk of zoonotic pathogens.

"We are currently sampling patients with enteric disease, respiratory disease, central nervous system infections and jaundice from six hospitals countrywide to gather data on the aetiology of these infections" says Stephen Baker. "We are working closely with local collaborators and partners, and hope that this will support the local research infrastructure and capacity building in healthcare systems to improve the diagnosis triage of disease", he continues.

To study how frequently individuals working with animals are exposures to zoonotic infection, the project team is longitudinally sampling people working with animals to study the potential for viral chatter between humans and their animals. This component of the project is following approximately 1,000 individuals that includes farmers, market workers, abattoir workers and is being conducted in 3 Vietnamese provinces.

### Do you have something to say?

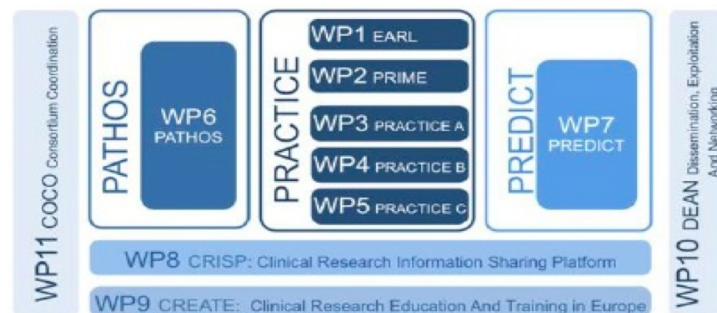
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provide access to expert advice and promote high quality, standardised research.

Ken Baillie has also recently been visiting colleagues in Tunisia as part of a WHO/ISARIC joint mission to discuss the SARI BSP in relation to nCoV, and an Jake Dunning also presented ISARIC and WHO'S collaborative efforts on MERS-CoV and SARI at the Public Health England Novel Coronavirus Conference, which was held in London in July 2013.

ISARIC was also represented at the H7N9 Conference and Workshop in Beijing and Shanghai in August, where Peter Horby presented the BSP and ISARIC ([see article above, left](#)).



## PREPARE-ing Europe for epidemics

*Kajsa-Stina Longuere and Adrian Wilder-Smith -*  
**ISARIC is, alongside several Europe-based member networks, taking on an active role within PREPARE, Platform for European Preparedness Against (Re-)emerging Epidemics. PREPARE is a large new European Commission funded (FP7) clinical research consortium aiming to address the urgent need to equip Europe against re-emerging epidemics.**

Awarded €24M over 5 years and led by Professor Herman Goossens at the University of Antwerp and

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Professor Menno de Jong, Amsterdam Medical Centre, PREPARE will kick off in January 2014, gathering 22 partners across Europe and Australia, 10 of these partners are also directly linked with ISARIC and ISARIC member networks. Menno will be at the ISARIC Meeting in September.

Aiming to improve preparedness, PREPARE offers a platform for key stakeholder within clinical research, diagnostics, ethics, data management and other interested parties to collaborate and create operational readiness for rapid deployment of clinical studies during an outbreak in Europe but with strong links to the rest of the world.

Inter-epidemic research aims towards optimizing clinical management of patients. PREPARE will enable harmonized, fit-for-purpose and large-scale clinical research studies. With five key objectives, experts in infectious disease preparedness from Europe and beyond will be united through 5 platforms: Pathos, Practice, Predict, Crisp and Create.

Briefly, the platforms are characterised as follows:

**PRACTICE** is the clinical and regulatory platform for conducting harmonized, large, effective, safe and clinically-useful patient oriented research and clinical trials in children and adults in Europe. Practice also includes ethics, administration and logistics.

**PATHOS** is the platform for pathogenesis research studies using systems medicine approach and aims to identify host and pathogen factors to severe disease development and to generate predictive algorithms to anticipate severity.

**PREDICT** is the platform that provides “State-of-the-Art” diagnostics and laboratory support for inter-epidemic clinical trials in PRACTICE and future ID outbreaks.

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**CRISP** is the IT platform that provides robust and reliable network to enable rapid data collection, secure storage, analyses and exchange of clinical data.

**CREATE** is the IT platform that aims to empower/ensure incorporation of clinical research and the results into optimized clinical practice as well as engaging interactions with main stakeholders involved.

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ISARIC Update

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