PRELIMINARY RESULTS

Pandemic Research Preparedness Survey of National Competent Authoritites and Research Ethics Committees across Europe

Contributors: JP Byrne[1], Maha Rahmani[1], Hugh Davies[2], Nina Gobat[3], Alistair Nichol[1] for PREPARE WP1
[1]University College Dublin, [2]Oxford Research Ethics Committee, [3]Cardiff University

Introduction

PREPARE WP1 conducted a short online survey to understand how prepared European National Competent Authorities (NCAs) and Research Ethics Committees (RECs) are to regulate and review clinical research protocols during a public health emergency. The following are some headline findings from the survey of 33 REC members and 11 NCA representatives.

Headline Findings

- NCAs and RECs across Europe are not uniformly ready to expedite review of clinical research in a public health emergency.
- All NCA and REC respondents consider it important that clinical research is conducted during a public health emergency.
- All NCA respondents agreed that clinical research should be regulated swiftly and 8 of the 11 NCA respondents said that fast-track approval was available in their country. However, respondents indictated a lack of clarity regarding the process for such review.
- 69% (20 of 29) REC respondents considered it important that ethics committees have pre-agreed processes for reviewing research protocols during a public health emergency. However, 29 of 33 REC respondents did not know or did not have a designated process for expedited review under these circumstances.
- 63% (17 of 27) of REC respondents agreed that regulating and reviewing research during a public health emergency, such as an infectious disease outbreak, raises novel ethical concerns.
- Survey responses indicate different ideas about what "expedited" review means and what time frames were realistic for emergency regulatory review.
- Pre or partially approved clinical research protocols were considered useful to speed up a clinical research response. However, such protocols were or are not routinely available, and respondents expressed need for guidance regarding standardising regulatory processes of such protocols.
- The findings point to an urgent need for engagement with regulators and RECs to provide EU and national level guidance on "best practice" for reviewing pandemic-relevant studies. These guidelines will need to consider the balance of risks and benefits for conducting pandemic-research, the need for urgency, accuracy, and maintenance of standards of care, the potential for strained resources and staff, the challenges to ethical review meetings and consent protocols, and ensuring European collaboration.

PREPARE is funded by European Commission grant number 602525

Objective

The Platform for European Preparedness Against (Re-)emerging Epidemics (PREPARE) is an EU-FP7 funded European network for harmonized large-scale clinical research studies on infectious diseases, providing real-time evidence for the clinical management of patients and informing of public health responses. Through Work Package 1, PREPARE is examining ethical, administrative, regulatory and logistical (EARL) barriers and solutions to conducting clinical research during an infectious disease (ID) outbreak. This survey aimed to understand how prepared European National Competent Authorities (NCAs) and Research Ethics Committees (RECs) are to regulate and review clinical research protocols during a public health emergency such as an ID epidemic or pandemic.

Participant Recruitment and Data Collection

Data were collected via LimeSurvey, an open source survey platform, during the months of March – July 2018. The data collection tool was developed iteratively and through piloting.

Participants were identified from publically available websites and personal contacts. For example, a list of National Competent Authorities (NCA) is located on the EMA website and corresponding NCA websites list their current members. An invitation for participation in this survey was sent to general emails for NCAs. Were possible, individuals involved in innovation, policy or vaccines were also identified and emailed directly. In total, 70 email invitations were sent to NCAs in Europe. To recruit members from REC members, a sample of REC members compiled for the doctoral research of a member of the EARL team (Sukumar 2018) was invited. An invitation to complete the survey was sent to over 300 individuals via email. Invitees were asked to forward on the email invitation to any suitable colleagues. Due to the purposive and snowball sampling methods used, response rates were not measured.

Results

Responses were received from 11 representatives of NCAs and 33 REC members across 23 European countries. Figure 1 maps the distribution of these responses in Europe. Figure 2 illustrates the total breakdown of completed responses by country. The REC members who respondent to the survey represent a range of different ethics committee types. These include academic institutes/universities (16), hospitals/university medical centres (6), national ethics committees (7), regional ethics committees (2), and a contract research organisation (2).

PREPARE is funded by European Commission grant number 602525

Figure 1: European Distribution of Respondents

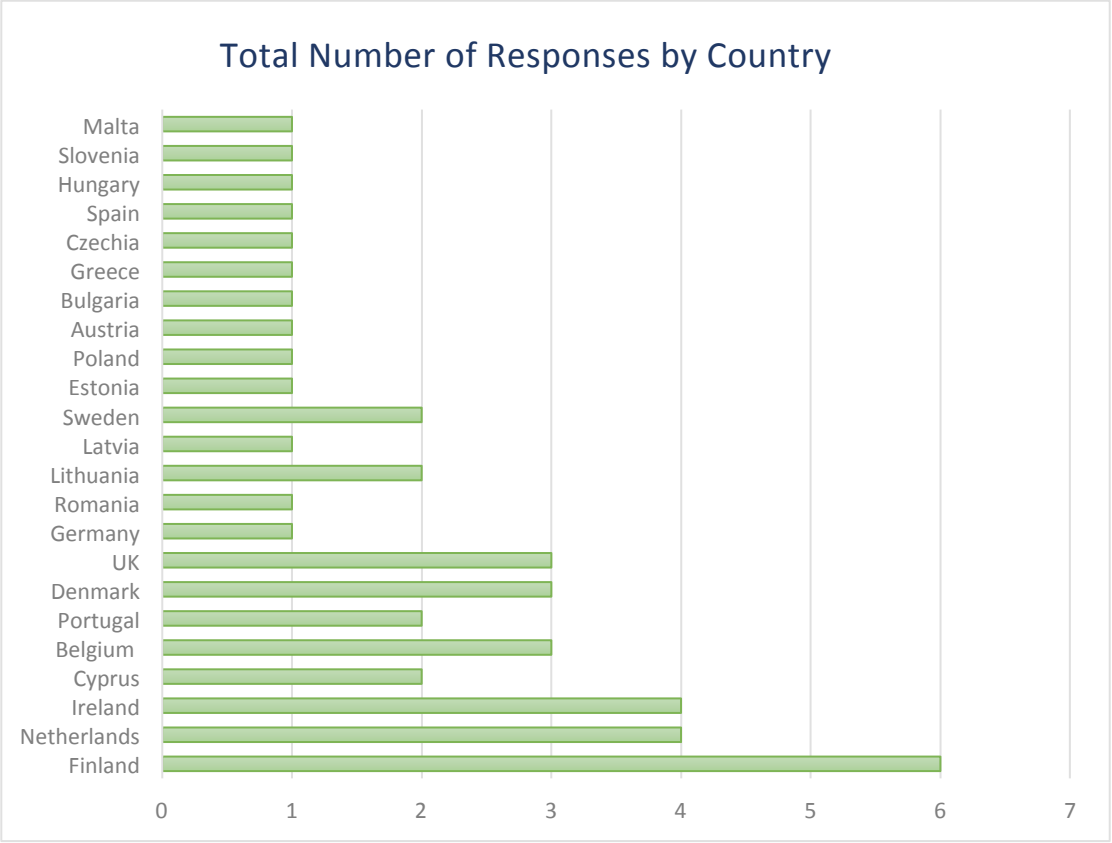

Figure 2: No. of Respondents by Country

PREPARE is funded by European Commission grant number 602525

Q1: Is there an option for obtaining fast-track or expedited approval for the conduct of clinical research in your country (e.g. during an epidemic or pandemic)?

Out of the 11 NCA members, 8 responded that fast track/expedited approval was available in their country (U.K., Spain, Denmark, Hungary, Belgium, Slovenia, Malta and Lithuania). NCA respondents from the Czech Republic, Ireland and Sweden did not consider that such a process existed or were not aware of one.

11 REC members indicated that fast track/expedited review processes were available for clinical research with their REC (Austria, Belgium, Bulgaria, Cyprus, Germany, Ireland, Netherlands, Poland, and the UK). The remainder of respondents said that expedited processes either did not exisit or that they were not aware of them.

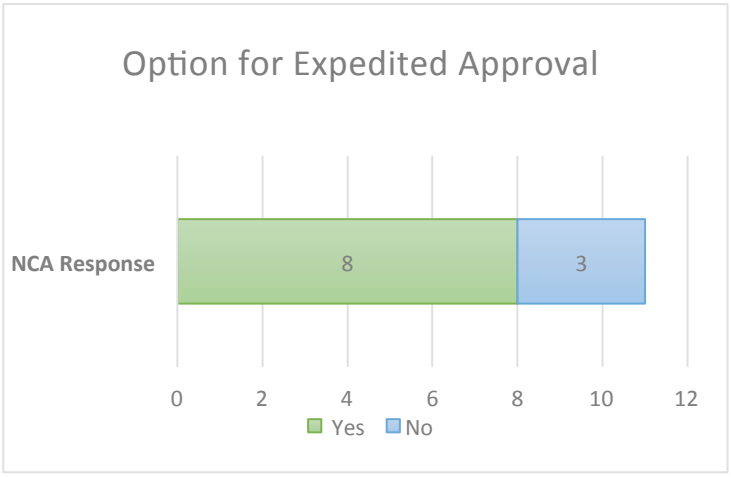

Figure 3

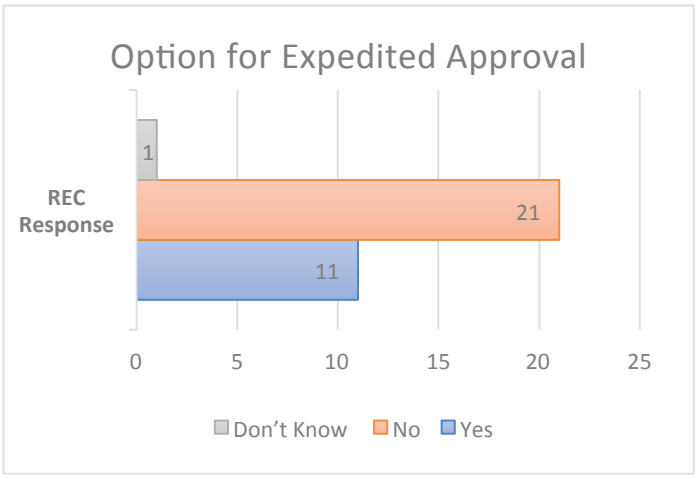

Figure 4

Of the 8 NCA representatives who indicated the availability of expedited review, 3 had had previous experience using this regulatory process (Belgium, Malta and the UK). The UK respondent described an expedited approval of vaccine trial volunteers in 3 days during the Ebola outbreak. The respondent from Belgium had experience using an expedited review during the 2009 H1N1 influenza pandemic. Fast track marketing authorisation of pandemic influenza vaccines was facilitated through accelerated assessment in the centralised procedure as part of the EMA's pandemic influenza crisis management plan.

Of the 11 REC members that indicated expedited approval was available, 8 noted that it had been used in the past (Austria, Bulgaria, Cyprus, Ireland, Netherlands, Poland and the UK). A respondent from a REC in the UK stated that "the expedited review process has been used on a few occasions in relation to public health emergencies, most recently this was in relation to Ebola where a CTIMP was given a favourable opinion in 5 days". In the Netherlands, it had been used for the H5N1 virus. A REC member from Austria noted that the review is done by the chairman and one specialist in the field (not by the entire committee, but this process has nothing to do with epidemics. A REC member from Poland stated that their REC had prepared within 5 days a full opinion about an emergency, experimental treatment program in case of epidemic disaster, however this epidemic never happened.

PREPARE is funded by European Commission grant number 602525

Q2: Does your NCA/REC have designated processes for the review and approval of clinical research during a public health emergency?

No NCA respondent could point to a designated process for regulatory approval of clinical trial research during a public health emergency. 4 REC respondents (in Cyprus, Ireland and the UK) stated that they have a designated process for ethical review during public health emergencies. The member from a REC in Ireland said that the chairman's action would be taken to expedite review, if necessary by an extraordinary meeting of the Ethics Committee. The members from UK RECs referred to the guidance from the Standard Operating Procedures of the UK Research Ethics Service. 29 REC members responded that either no designated process exists or they were unsure.

Q3: Did you regulate/approve any clinical research during an infectious disease outbreak (e.g. Ebola, H1N1, Zika)?

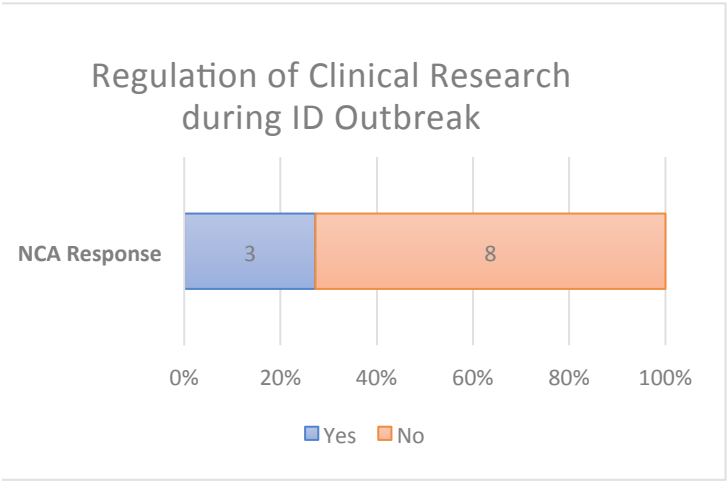

Figure 5

3 NCA representatives had experience of regulating clinical research during previous ID outbreaks (in UK, Czechia and Belgium). The UK respondent described work on Ebola vaccine trials and influenza vaccine approvals via a centralised EU procedure. The respondent from Czechia regulated trials during the H1N1 influenza outbreak and Belgium had experience mainly with phase 2 and 3 trials on safety, efficacy and immunogenicity of vaccines during the Ebola and H1N1 outbreaks.

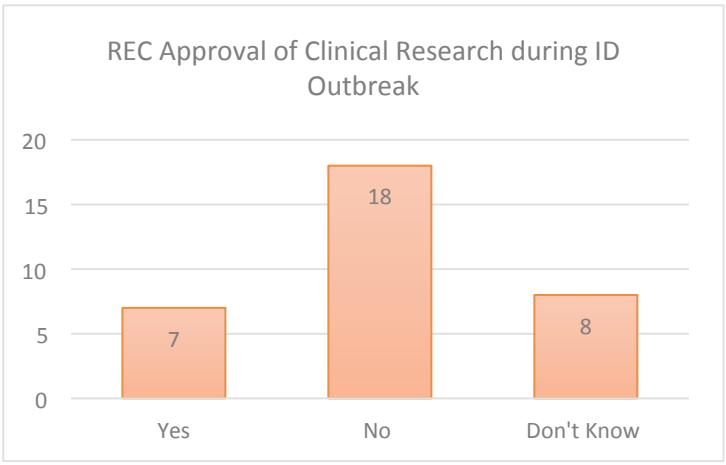

Figure 6

The 7 REC members who had experience of approving research during an ID outbreak were from Belgium, Finland, Netherlands and the UK. Belgian respondents described an approval for PCR research for influenza detection by mouth swabs, and a protocol for quick approval for the avian flu, which was solved in 48 hours. In the Netherlands approval was granted for H5N1 many years ago but the trial did not start. The UK REC member stated that approval was granted for Ebola research. A respondent from Finland said that approval had been granted for an influenza medication clinical trial.

PREPARE is funded by European Commission grant number 602525

Q4: Does your NCA/REC approve "sleeping" protocols for research to be conducted during an infectious disease outbreak?

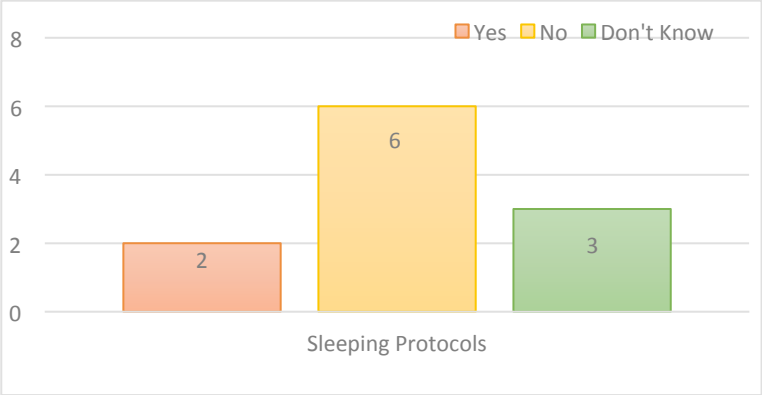

Figure 7

Respondents from NCAs in Denmark and Malta noted that they approve sleeping (pre- or partially approved) protocols. Respondents from NCAs in the UK, Ireland, Czechia, Hungary, Belgium and Slovenia do not approve sleeping protocols and those from Lithuania, Spain and Sweden did not know if these were possible.

Figure 8 shows the REC members responses to Q4. 7 REC members responded that they did not know if sleeping protocols could be approved. These were from Bulgaria, Finland, the Netherlands, Poland, and the UK. 22 REC members (from Austria, Belgium, Cyprus, Denmark, Estonia, Finland, Greece, Ireland, Lithuania, Latvia, Netherlands, Portugal, Sweden, and the UK) responded that sleeping protocols were not approved by their REC.

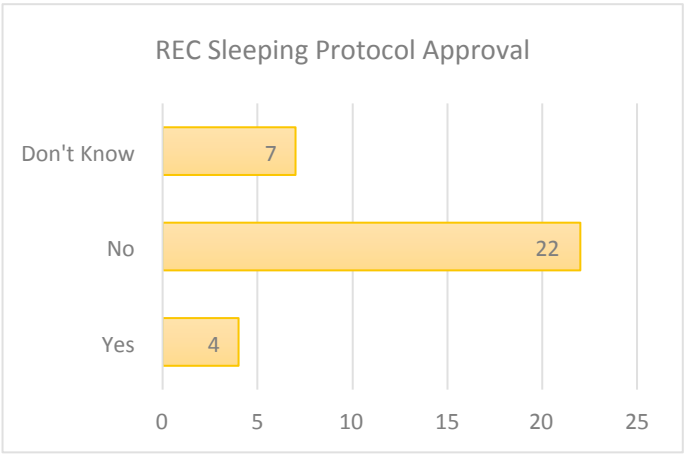

Figure 8

The member from Greece along with their response also stated that "The case of sleeping protocols has not taken place so far…however to proceed with such an approach more detailed discussions will have to take place with [national ethics committee] in order to see how feasible this is and risk evaluation to be performed". The countries in which REC members responded that sleeping protocols are approved for research during an ID outbreak were Belgium, Finland, Germany, and Romania.

Q5 asked respondents their views on clinical research conducted during an ID outbreak.

40 individuals (29 REC, 11 NCA) agreed that "it is important that clinical research is done during an ID outbreak."

All NCA respondents (11) agreed with the statement "It is important that clinical research is regulated swiftly during an outbreak".

20 REC members agreed with the statement "It is important that ethics committees have pre-agreed processes for reviewing research protocols during an ID outbreak". 9 REC members disagreed this statement and 4 did not answer. A REC member from Finland noted "this is not a question on pre-agreement amongst RECs; it must take place according to the regulations". A REC member from the UK also stated that "whilst this is something that we haven't done to date, it is something that we would be willing to do".

PREPARE is funded by European Commission grant number 602525

All NCA respondents (11) and 17 REC members agreed that "reviewing research during an ID outbreak raises novel ethical concerns". 10 REC members disagreed.

Q6: What are your concerns when considering the regulation and ethical review of clinical research during an infectious disease outbreak?

23 REC members and 8 NCA representatives responded to this question. Respondents highlighted a range of concerns when considering the ethical review of clinical research during an ID outbreak. These include;

Balancing Need for Urgency, Ethics, Efficacy & Safety

The need to generate robust, ethically sound data under constrictive time constraints. The regulation of research during an ID outbreak requires a close examination of individual research projects' design and conduct, but decisions need to be taken swiftly whilst also ensuring the safety of all participants. Consequently, there is a need for accuracy, expertise, meetings and approvals within very short timeframes, alongside the maintenance of ethical vigour and standards of care. This involves the balancing of the risks (safety, efficacy) and benefits (clinical, scientific) of research with the protection of vulnerable participants in a context where public pressure to find solutions and effective therapies may have an impact.

Pressurised Structures, Services & Risks

An ID outbreak will undoubtedly mean pressures and disruption to healthcare resources structures and services. This may impinge on sites' ability, or willingness, to conduct trials. Risks associated with research should be proportionate to severity of outbreak and different research designs will present different ethical issues (e.g. use of placebos). During an ID outbreak there may be an increased risk of therapeutic misconception as it will be an emotive time, pressure on staff to rush process, or seek non-requirement of consent. There will also be an inevitable impact of strained resources on staff time and priorities and potential need to protect staff from any fall-outs from research during an emotive time.

Time Sensitivity and the Need for European Collaboration & Guidance

Sleeping protocols were identified as potentially useful. However, due to time-sensitivity of pandemic-research there is a need to start research once the protocol and informed consent material are approved by a REC – without waiting for other study centres. Yet, the set-up and regulation of pandemic-relevant research often involves more than just RECs. For example, multi-site trials require contracts, sponsors, site initiation visits etc. – how do these interact with sleeping protocols?

Some respondents noted the importance of European collaboration and coordination in the form the European Medicines Agency (EMA) to facilitate "real-time regulatory networking" and expedite reviews of pandemic products (e.g. flu vaccine), and the Clinical Trial Facilitation Group to progress the idea of sleeping protocols. Furthermore, there was an identified need for guidance from national legislation or ethics committees to assist SOP development and provide guidelines on fast-track reviews (alternative meeting formats, non-requirement of physical presence) within an emergency research response context.

Concluding Remarks

According to the responses to this survey, NCA representatives and REC members believe it is important that clinical research is done during an ID outbreak and it should be regulated as swiftly as possible.

Despite 69% (20) of REC members thinking it is important that RECs have pre-agreed processes for the ethical review of research during an ID outbreak, RECs across Europe are not uniformly ready to expedite reviews. 8 of the 11 NCA respondents stated that there was an option for obtaining expedited approval for clinical research. However, only one-third of REC respondents stated that fast-track/expedited approval was possible within their REC. Even where this option was deemed available, there was a varying perception of what "expedited review" might mean (e.g. both "72 hours" and "30 days" were noted) and how to

PREPARE is funded by European Commission grant number 602525

operationalise it. In general, respondents noted a reliance on standard REC timeframes and processes for the ethical review of research during a public health emergency.

Where expedited reviews are available, these are often reliant on REC chair/president taking action to review the research themselves (sometimes in collaboration with a specialist) followed by a post-hoc review or calling of an extraordinary review meeting if required. These responses highlighted the prominence of ad hoc actions and authority of individuals rather than pre-specified standard operating procedures (SOPs). Terms like "whenever needed", "use of conference call", "it is possible to arrange an extra session", and "additional meetings may be arranged to provide shorter timelines", indicate the improvised nature of these expedited reviews. For most NCA respondents (5) the fast-track approval process was facilitated rather than formally specified. Expedited reviews are understood to be an important option but generally managed on a case-by-case basis rather than through a laid-out standard operating procedure (SOP), as indicated in the following statements;

> "There is no formal statement in the legislation, however there is agreed position within the National Competent Authority to have the option for expedited approval of clinical trials on case-by-case basis".

> "[We are] willing to provide fast track approval, e.g. in case of a public health emergency. This would be decided on an ad hoc basis, as there are currently no supportive regulations/procedures".

Only two REC respondents identified pre-specified SOPs for the fast-track review of clinical research. Both respondents were from national ethics committees in the UK & the Netherlands and described instances of using these processes in context of ID outbreaks; in relation to Ebola research in the UK and a H5N1 trial in the Netherlands. Similarly, NCA representatives from the UK and Belgium described the use of expedited regulation during previous ID outbreaks.

A small number of REC respondents believe that if the standard REC processes work quickly and efficiently, the context of a public health emergency may not require a specific review process, especially if the research design is already ethically sound. To further illustrate the complexity of this issue, 37% of REC respondents (10 out of 27) do not believe reviewing research during an ID outbreak raises novel ethical concerns while 63% (17 of 27 respondents) did. This raises important questions for pandemic-research preparedness strategies regarding how to highlight the novel ethical considerations of pandemic-research – even for well-equipped and efficiently functioning RECs, and the shared responsibility for potential bottlenecks in research design and regulatory processes.

These findings point to an urgent need for engagement with regulators and RECs to provide EU and national level guidance on "best practice" for reviewing pandemic-relevant studies. These guidelines will need to address the balance of risks and benefits for conducting pandemic-research, the need for urgency, accuracy, and maintenance of standards of care, the potential for strained resources and staff, the challenges to ethical review meetings and consent protocols, and ensuring European collaboration.

Comments welcome: contact jp.byrne@ucd.ie

Report prepared by JP Byrne and Maha Rahmani on behalf of PREPARE WP1
Report date: 14 September 2018

PREPARE WP1: Alistair Nichol[1] (lead), Christopher Butler[2], Nina Gobat[3], Micaela Gal[3], Nicholas Francis[3] Angela Watkins[3], Kerry Hood[3], Ronald Moore[1], JP Byrne[1], Prasanth Sukumar[1] and Steve Webb[4].

[1]University College Dublin, [2]University of Oxford, [3]Cardiff University, [4]University of Western Australia

PREPARE is funded by European Commission grant number 602525