PREPARE

EARL: Ethical, Administrative, Regulatory and Logistical solutions

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Disclaimer

This report represents a rapid assessment for the PREPARE project. The research was conducted between February 2014 and early July 2014 and presents the most up to date and accurate information available across the European Member States. The research team recognises that the assessment may contain some inaccuracies or gaps because of the limitations of such things as time and logistics. It is however, designed as a 'live document' and represents the first undertaking of its kind. As such, the report will be continually refined and added to at regular intervals, as new, and or, appropriate information becomes available. With that in mind, we welcome any additional relevant information readers may have, now or in the future, that will enhance its reliability as a resource for researchers in the field.

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The authors contributed to and commented on aspects of the methodology, protocol development, fieldwork and data analysis as part of the operational research team based upon the participation in weekly team meetings and/ or telephone conferences.

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GLOSSARY

CA – Competent Authority

CAPNETZ - Community-Acquired Pneumonia Competence Network

CCMO - Central Committee on Research Involving Human Subjects (Netherlands)

COMBACTE - Combatting Bacterial Resistance in Europe

CTA – Clinical Trial Application

EARL - Ethical, Administrative, Regulatory and Logistical requirements

EC – Ethics Committee

ECRIN - European Clinical Research Infrastructure Network

EFGCP - The European Forum for Good Clinical Practice

EFPIA - European Federation of Pharmaceutical Industries and Associations

EMA – European Medicines Agency

ESICM- European Society of Intensive Care Medicine

EU – European Union

EUREC - European Network of Research Ethics Committees

GDP - Gross Domestic Product

GP - General practitioner

GRACE - Genomics to combat Resistance against Antibiotics in Community acquired LRTI in Europe

HRA - Health Research Authority

HTA - Human Tissue Authority

ICU – Intensive Care Unit

ID - Infectious Disease

IMI - Innovative Medicines Initiative

IMP - Investigational Medicinal Products

IQR - Interquartile Range

ISARIC - International Severe Acute Respiratory and Emerging Infection Consortium

MEP - Member of the European Parliament

PENTA-ID – Paediatric Infectious Disease Clinical Trial Network

PREPARE - Platform for European Preparedness Against (Re-) emerging Epidemics

REC – Research Ethics Committee

SOP – Standard Operating Procedure

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

UTC - Coordinated Universal Time

WHO – World Health Organisation

EXECUTIVE SUMMARY

As part of the Platform for European Preparedness Against Emerging Epidemics (PREPARE), this first report from Work Package 1 (WP 1) sets out a preliminary assessment of the Ethical, Administrative, Regulatory and Logistical (EARL) landscape for the conduct of PREPARE's clinical studies in Europe. PREPARE has many objectives, however, this report focuses on the challenges PREPARE will encounter as it conducts clinical trials in primary care, hospitals and intensive care units during inter-pandemic and pandemic periods.

This report is designed as a dynamic document and has been prepared to meet the requirements of the WP1 EARL Task 1.1. 'Rapid Assessment' (due at month 4 of PREPARE). This task includes the mapping current EARL practices in Europe, and an early scoping exercise to begin to identify potential EARL barriers to conducting research including clinical trials and observational studies in Europe.

The aim of this initial WP1 'Rapid Assessment' report is to provide a preliminary indication of EARL barriers to setting-up and conducting research in different European countries.

It should be noted that this initial report is not comprehensive and is intended as an early-stage rapid reference for PREPARE researchers. The report will form part of an on-going process which will be continually updated with information throughout the lifetime of the PREPARE project.

This report consists of:

- A description of competing issues across Europe which impact EARL requirements and a summary of research in this area to date.
- Country data reports collected from data searches and secondary data.
- A survey of research experience from key European network / research leaders.
- Qualitative Interviews with PREPARE Stakeholders.

Preliminary results

The findings from research to date have identified potential barriers to research in pandemics including the time frame involved in gaining ethics approval, the lack of availability of clinical staff in the event of pandemic difficulties, issues related to consent, randomisation, and communication between research groups and the public. Proposals include securing pre-approval for research, assigning dedicated research co-ordinators to projects within institutions, ensuring increased engagement with the public and producing standardised protocols.

Currently Public Health Research remains the best model on which to base research projects, with pre-approval and established protocols in place in the event of an outbreak.

Two key areas of legislation, both currently under review in Europe (the Clinical Trials Regulation and the Data Protection Regulation), pose significant challenges but may also provide potential direction to many current EARL issues. The Clinical Trials Regulation may in the future significantly reduce the logistical and administrative burden of future ethical submissions by centralising submission but will impose specific requirements on research groups that must be adhered to. The current Data Protection Directive is interpreted quite differently across Europe leading to a variance in the levels and type of consent required across countries. Future changes to this legislation may either provide increased clarity and uniformity on this issue or may impose such strict requirements that certain types of research will become unfeasible. Potential exemptions may exist and an understanding of these key legislative areas will help troubleshoot potential problems in the future.

Country data: A key initial finding is that information needed by clinical researchers to conduct multi-centre research in Europe is largely fragmented (between countries and even within some countries) and often either not easily accessed or in some cases unavailable. Thus establishment of comprehensive country data reports will serve as a useful conduit to allow the PREPARE clinical

Work packages to rapidly identify potential challenges in conducting research in all PREPARE EU countries.

Survey data: Practical experiences of active European clinical researchers were surveyed. The data showed significant country differences but many common areas of concern were identified. For example, a pattern of increasing delays in the receipt of approvals (ethical, competent authority, contracts etc.) needed to commence any European research project, and of note many reported that the delays were longer than advised by the governing institutions. Several countries identified that obtaining ethical approvals for observational research is quicker and simpler that obtaining approvals for clinical trials. Recommendations included developing access to fast track and pre-approval processes. Public reaction was also identified as being likely to have an influence on the ease of conducting research during a pandemic or epidemic. Fear and mistrust of research processes, in particular with vulnerable groups, and in ethnic minority groups were identified as possible barriers to participation. Provision of clear information, research promotion and engagement with the media were potential strategies suggested to enable public participation. The key finding across countries however was concern that clinical staff would not have the time to complete research in the event of a pandemic.

Interview data: The interviews revealed socio-cultural barriers as an important factor across member states. Country, regional, sub-regional and institutional differences were highlighted as were professional, culture and working practices. This data confirmed many of the perceived problems as well as possible solutions to EARL. Non-uniform ethical approvals and (disparate approval processes) again emerged as major issues. The need to address problems associated with rapid response and pre-approved protocols were also discussed with some cross-cultural examples of how current practice has helped expedite research in some jurisdictions. In addition cultural specific challenges in recruitment and the importance of ensuring adequate public education was highlighted in the context of recruitment. The ability and variation in what is understood to be required in obtaining valid informed consent varies across countries depending on interpretation of data protection legislation within member states. The

importance of established professional networks, led by experienced experts emerged strongly as a key element in improving conduct of research in terms of gaining governmental support, ethical approval and improving recruitment. Staff also identified inherent staffing problems in research. Costs, funding and intellectual property was also candidly addressed in the interviews and revealed potential blockages to effective research.

Triangulated data: The findings identified key areas that present problems in relation to research preparedness during epidemics / pandemics and opportunities for solutions, many of which are reflected in research carried out to date. The lack of uniformity regarding ethics procedures was a common theme. The variance in procedures amongst and within countries in addition to the actual time frames indicates that pre-approval of research is essential to the feasibility and success of the project. Significant focus must be given to the classification of the research from the outset as this will exponentially effect the logistical and process issues involved at many levels of the of research. In addition careful consideration of issues related to public engagement, processes of recruitment, clarification of appropriate levels and methods of consent and allocation of funding resources will be required in advance.

INTRODUCTION

EARL

One of the many challenges of conducting high quality, large-scale clinical research is ensuring compliance with all necessary Ethical, Administrative, Regulatory and Logistical requirements (EARL). Examples include navigating the administrative processes needed to obtain the required research governance approvals in various countries; development of standardised protocols; ensuring an appropriate flow of research funds; and meeting human tissue authority (HTA) requirements for clinical and biological samples. In the event of severe Infectious Disease (ID) outbreaks, these EARL requirements make it extremely difficult, if not impossible, to implement clinical research studies during a pandemic or epidemic. While many of the bottlenecks are structural, social and cultural factors also play an important role. Identifying and implementing solutions to the EARL bottlenecks is therefore crucial in making the PREPARE network ready to rapidly implement clinical research for any severe ID outbreak.

Who We Are

EARL Work Package 1 (WP1) is led by Alistair Nichol from the University College Dublin (UCD) and includes a team of researchers from University College Dublin, Cardiff University and the University of Western Australia. The EARL WP is aimed at identifying and implementing solutions to key structural bottlenecks and cultural and behavioural barriers to the rapid implementation of large multi-site clinical studies in Europe in response to severe ID outbreaks.

What We Hope To Do

In WP1, we will identify and propose solutions to EARL issues. Steps towards this will include; gathering information about current EARL procedures in EU member states and associated countries, gaining an insight of the actual practicalities and bottlenecks of navigating these processes as perceived and experienced by researchers who have set-up and conducted clinical research within and across European countries, and obtaining an understanding of cultural and behavioural barriers that may be pertinent to conducting research

in each European Country. Information will be gathered into an on-going live document that will be shared with and contributed to by PREPARE partners, European researchers, research ethics committees, European policy makers and the other organizations (i.e. the World Health Organization).

Our Approach

We plan to be comprehensive in developing solutions for all EARL processes potentially encountered by PREPARE. This includes addressing:

- All age groups and study cohorts (including children, vulnerable groups and unconscious critically ill patients);
- All relevant clinical settings encompassing patients in Primary Care, Hospital Care and Intensive Care Units;
- All European Member States, and later EU associated countries;
- Various study types including clinical trials and observational studies (with and without biological sample collection), the nature of which is outlined in the relevant PREPARE work packages.

Our approach is calibrated to account for severe Infectious Disease (ID) outbreaks that represent different levels of threat to public health and takes into account the full range of infectious syndromes that are plausibly associated with potential severe ID outbreaks. The key element of the approach to ethical, administrative and regulatory (EAR) issues is securing prior approval. The key element of the approach to Logistic (L) issues is prior planning of research responses with development of coordinated research capacity and the inter-epidemic conduct of clinical research to continually test and refine these processes.

Summary of EARL Objectives

To identify and implement 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. This will include;

1. Mapping current EARL practices and procedures in Europe, identifying EARL bottlenecks as well as potential PREPARE synergies for the conduct of clinical studies during both inter- and intra-epidemic periods;
2. Developing and implementing both immediate pragmatic solutions to facilitate the effective conduct of the PREPARE studies, as well as, provide medium / longer term solutions to overcome the identified bottlenecks;
3. Determining the effectiveness and impact of EARL solutions, to ensure continuous improvement in the PREPARE EARL framework.

PREPARE Overview

The Challenge of research in Infectious Disease Outbreaks

Infectious disease (ID) outbreaks are among the greatest threats to human wellbeing and prosperity. Global movement of people and goods is accelerating and an individual can travel anywhere in the world in less time than it takes for many common human pathogen's to incubate. Without rapid detection and containment, ID outbreaks can develop into epidemics and pandemics. Outbreaks tend to arise with little warning, spread quickly and end abruptly. The 2009 H1N1 influenza pandemic spread to six continents in 3 months and infected between 11% and 21% of the world's population. In contrast to the speed of an epidemic or pandemic, establishment of research can take months or even years, so that by the time a trial is ready to start the outbreak is over. Therefore, whilst the 2009 pandemic would have provided a perfect opportunity to conduct research, virtually no patients were enrolled into clinical trials and as a result the optimum treatment of this pandemic strain remains unknown.

During the pandemic, millions of people were treated with Oseltamivir (Tamiflu) however the limited evidence for the effectiveness of Oseltamivir in critically ill patients stems from retrospective observational studies (Flannery and Bastin., 2014). If a clinical research trial had been conducted during this pandemic, enough participants could have potentially been recruited in one day alone to ascertain the required evidence of its effectiveness and optimum-dosing regimen obtained. While clinical samples were collected and stored during the pandemic, this was completed for the purpose of clinical diagnosis only. These samples would be invaluable for research to inform future pandemics; however, they cannot be accessed, as the required consent for research was not obtained at the time the samples were collected.

Randomised Controlled Clinical Trials are the recognized gold standard for obtaining evidence for the effectiveness of a treatment. The currently available treatments for influenza include antivirals such as Oseltamivir, Zanamivir and Peramivir (authorized for emergency use), and potentially other treatments such as steroid hormones. However, it is not known what impact these treatments may have in the groups who are likely to experience the most serious infections

in pandemics such as children, pregnant women, the elderly or immunocompromised, or if they are actually effective against a pandemic strain of flu. To gather the required evidence it is imperative to conduct rigorous randomised controlled trials enrolling patients during a pandemic.

Currently models of organised rapid response approaches exist in public health, for example those set up by Centre for Disease Control in America to respond to Salmonella outbreaks. These include pre-approved protocols and standardised case report forms that can be taken 'off the shelf'. Standardisation of procedures and ease of data collection will be vital for conducting pandemic research.

In designing any pandemic research, it is important to obtain a thorough understanding of the 'signature features' so that all eventualities are considered and planned for. Important insight can be obtained using evidence from past pandemics characterised by shifts of virus-sub-type, successive pandemic waves, differences in impact in different geographic regions, and shifts in death rate to younger or unexpected (pregnant women) populations (Miller *et al*, 2009).

Initiatives Aimed at Pandemic Research (ISARIC)

Some measures are currently in place to aid pandemic research. One of these initiatives is the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC); a global alliance formed in December 2011, which now includes 60 research networks, over six continents. ISARICs aim is to ensure that effective global research can be carried out during epidemics. This involves setting up relationships and trust with researchers, training of personnel, and obtaining approved protocols and strategies during the 'peacetime' periods so that research can start immediately an epidemic / pandemic is confirmed. The aim is to store data and end results in a freely available repository. ISARIC is involved in PREPARE, and EARL researchers will link and liaise with ISARIC in order to benefit from the experience and information already gained in that group.

Europe Not Prepared

Extensive pandemic and epidemic preparedness systems, including those for the conduct of research, are needed to protect health and socio-economics in the EU and globally. Much progress has been made in the design and development of appropriate structures and procedures for rapid and adequate ID outbreak public health response measures by national and international health authorities. Likewise, preclinical research responses to severe ID threats and outbreaks by the scientific research community (e.g., epidemiological, microbiological, immunological and genetic research) has also made important progress during the last decade in terms of the ability to respond rapidly to ID outbreaks. However, this is in sharp contrast to the clinical research response, which is often delayed, isolated and fragmented, having, as a consequence, little to no impact on improving patient outcomes, and critically limiting the ability to develop high-quality evidence to inform clinical management strategies. PREPARE's mission is to address this gap by establishing a European clinical research framework for harmonised large-scale clinical research studies on infectious diseases, prepared to rapidly respond to any severe ID outbreak, providing real-time evidence for clinical management of patients and for informing public health responses.

Difficulty in Conducting Research during Epidemics/Pandemics

An epidemic or pandemic can cause chaos and research quickly becomes very difficult. Clinical staff may fall ill themselves compounding the shortage of staff. Farrar suggests that an intervention squad is needed who are resourced, trained and ready to carry out research in the event of an epidemic and in the meantime doing routine hospital work during peacetime (Yong, 2012).

Many EARL issues and bottlenecks in conducting research during an epidemic/pandemic are similar to those encountered when conducting general ID research. Aspects that will have significant more impact include the time that it takes to obtain research approval and set-up processes. Further issues that will more severely affect the conduct of pandemic research include rapid access to laboratory facilities and a lack of rapid diagnostics. Additionally, the potential participant's perception of risk and benefits, knowledge and trust during an

epidemic/pandemic period would affect their willingness to be enrolled. While the principles and values of international ethics guidelines and human rights statues must be upheld, there should be consideration given to processes that would expedite research in emergency situations.

It will be crucial to establish flexible mechanisms around EARL procedures and streamline processes across and within Europe. Fast-track review and approval by ethics and other required boards, pre-approved and universally recognised protocols and patient-facing documents (information and consent forms), and a network of trained research-ready staff would be an absolute requirement to conducting pandemic/epidemic research. Furthermore, in order to be able to rapidly initiate meaningful clinical research of any kind, in response to any kind of severe ID outbreak, up-and-running pan-European clinical networks covering the full breadth of clinical care from primary care to hospital wards to ICUs, from virologists to GPs to ID specialists and paediatricians is crucial.

Social, Economic and Cultural Influences on Pandemic Research

Pandemics and epidemics are likely to disproportionately impact the most vulnerable or at-risk people in communities as well as marginalized populations. In addition to medical risk, social, economic and cultural aspects must be taken into account in the planning and feasibility of conducting epidemic and pandemic research. EARL will ascertain these barriers to conducting pandemic research and identify solutions. Consideration will also need to be given to how PREPARE will integrate with Public Health Pandemic / Epidemic responses for example how research information would fit into the 'WHO Outbreak Communication' procedures. This will be an on-going task of the EARL WP.

Existing Evidence of Research Barriers during a Pandemic

A useful insight into the main hurdles into designing and conducting a randomised trial for pandemic critical insight is given in Annane *et al* (2012). This French multicentre double-blind trial examined use of corticosteroids in intensive care unit (ICU) patients with 2009 H1N1 influenza pneumonia who required mechanical ventilation. The study analysed the feasibility and difficulties in designing and initiating a trial during a pandemic. The study details how long the

different stages of the trial set-up and conduct required, and suggests potential improvements and estimated time savings. The results revealed that all study approvals were obtained within 4 weeks. The drug and placebo were manufactured and dispatched to hospitals within 6 weeks. However the peak of the influenza wave was missed by 2-3 weeks and only 26 patients out of 205 patients were randomised. The main reasons cited for non-inclusion were patient's admission occurring prior to the trial start and ICU staff being overwhelmed with clinical duties. Steps that were suggested that may have led to earlier study start-up were: parallel rather than sequential regulatory approval, preparation and masking of study drugs by local pharmacists and a dedicated research team in each centre.

Burns *et al* (2013) carried out a cross-sectional survey to characterise clinical research activity in ICUs during the 2009 pandemic. They aimed to characterize clinical research activity during the influenza pandemic to understand the experiences, beliefs, and practices of key stakeholders (139 ICU administrators and 39 research coordinators) involved in the implementation of pandemic research. While the researchers and administrators supported participation in pandemic ICU research, several barriers were identified. The research coordinators placed significantly greater importance on the participation of their ICU in pandemic research. Both administrators and coordinators expressed a need for rapid approval processes, designated funding for research personnel, adequate funding for start-up and patient screening, pre-approved template protocols and consent forms, and clearer guidance regarding enrolment. Coordinators acknowledged the need for alternative consent models to increase their capacity to participate in the next pandemic. More administrators expressed willingness to participate in research during a future pandemic providing the required research resources were made available to them. The study concluded that pandemic research preparedness planning with regulatory bodies and dedicated funding to support research infrastructure, especially in community settings' were required to optimise future participation in pandemic research.

Challenges to conducting research during pandemics are also covered in a 2010 publication (Fowler *et al*, 2010). This includes the need for centralised REC

boards, pre-existing case report forms, universally agreed case definitions, widely available standardised diagnostic testing that is sensitive enough in critically ill patients, availability of trained personnel, suitable funding opportunities, and good communication within established research networks.

The Canadian Critical Care Trials Group project conducted a pilot trial, 'The collaborative H1N1 Adjuvant Treatment (CHAT trial)', to investigate the feasibility of conducting a trial during a pandemic (Burns *et al*, 2011). The aim of this pilot is to inform the design of a larger trial that would be conducted during a pandemic. Several models of informed consent are proposed including *a priori* consent from a substitute decision maker (relative or legal guardian of the potential participant), waived and deferred consent. The pilot study included adult ICU patients in Canada, Saudi Arabia, Mexico, Argentina, Australia and New Zealand. The primary objective was the ability to recruit the desired patient populations under pandemic conditions. Secondary outcomes included adherence to medication regimen, ability to collect endpoints for a full trial, number of consent withdrawals and the impact of approved consent models on recruitment rates. Conclusions around study design challenges included the need to centrally randomise, preservation of allocation concealment, ensuring that study blinding compare to a matched placebo and the use of novel consent models. Furthermore, implementation requires that the trial design is pragmatic and initiated in a short time period amidst uncertainty regarding the scope and duration of the pandemic.

The World Health Organisation conducted a technical consultation report, 'Research Ethics in International Epidemic Response', (2009) which also provides useful information on practical options to facilitate ethical approval research in epidemics. These include fast track review of emergency research, adjusting the balance between in-person and electronic communications by REC members, the use of pre-emergency repositories of study protocols or protocol parts that could be pre-screened by RECs on a national level, retrospective rather than prospective ethics review (with safeguards in place to address non-compliant or sub-standard research conduct).

Cook (Cook *et al* 2010) also proposes recommendations to researchers and ethics

committees on pandemic-related critical illness. Strategies that expedite and centralise RECs and alternative consent models are considered.

A review of demographic and attitudinal determinants of behaviours during a pandemic has also been conducted (Bish and Mitchie, 2010). The objectives of the review were to identify the key demographic and attitudinal determinants of types of protective behaviour during a pandemic and to describe a conceptual framework in which to better understand these behaviours and to inform future communications and interventions in future influenza pandemics. The research highlighted the existence and impact of demographic differences on behaviour. No evidence of barriers to conducting pandemic research was found for primary care settings. The majority of research and prospective protocols are done for the ICU and secondary care emergency settings where the majority of the burden of severe disease occurs.

Table 1: identified barriers to conducting research during pandemics

Research Area and Barriers	Proposed solution
Enrolling patients: Lack of clinical staff time during pandemic.	Dedicated research coordinator to explain study to potential participants and screen patients for eligibility on a daily basis in ICUs. Attending physician to confirm eligibility for participation.
Consent: RECs may not permit alternative consent models. Difficulty in obtaining consent as patient too ill, family member not contactable, ill themselves, no access.	Patient enrolled and consent deferred to a substitute decision makers or the patient (whoever can provide consent first) when it is not possible to obtain consent within 24 hours. Consent in person or by telephone. If a patient dies before providing consent, request permission from RECs to include data collected during participation. Pre-approved consent models.
Randomisation.	Randomisation lists provided by the study centre. Research pharmacist to assign critical patients to treatment arms.
Protocolising and documenting study co- interventions e.g. ventilation, and general clinical management.	It is likely that co-interventions cannot be protocolised under pandemic conditions. Decisions of primary clinician should be documented. Merging study data with an influenza registry as in CHAT could do this, or data capture on unique forms.
Non-standardised diagnostic testing. Lack of rapid tests with required sensitivity to identify suitable participants.	Universal protocol, which must be established and followed by all local and central laboratories. The test must have evidence of sensitivity in all possible patient groups (e.g. children, critically ill). In addition to the actual testing, a protocol for the type of samples, timing of samples, labelling, shipping and recording of results must be approved and in place.
Fast-track, pre- prepared and approved study documentation.	Universally agreed case definitions, pre-approved protocols, case report forms, data collection forms, adverse event reporting.
Inclusion / exclusion criteria.	Justification for including vulnerable subjects and justifications for exclusion.
Unknown and unpredictable scope and duration of epidemic / pandemic.	Gather information about past pandemics from existing literature. Recognise and plan for all possible eventualities.
Clinicians would not permit enrolment into blinded RCT (e.g. critically ill, previously well child)	Open label treatments.

Lack of understanding of research by potential participants, therefore limiting participation	Good communication strategy, dedicated person to explain study, clear and targeted information documents.

Current Research Environment

The EU clinical trials Directive 2001/20/EC

Clinical trials performed in the European Union are conducted in accordance with the Clinical Trials Directive. The European Clinical Trials Directive 2001/20/EC was introduced in 2004 to establish standardisation of research activity in clinical trials throughout the European Community. The Directive provides a framework, which sets out how clinical trials investigating the safety or efficacy of a medicinal product in humans must be conducted. It includes medicinal trials with healthy volunteers and small scale or pilot studies. The Directive aims to provide greater protection to subjects participating in clinical trials, ensuring quality of conduct and harmonising regulation and conduct of clinical trials throughout Europe.

Problems with the Clinical Trials Directive 2001/20/EC

The Directive 2001/20/EC introduced in 2004 is widely acknowledged to have reduced the attractiveness of the EU for conducting clinical trials. Implementing the Directive introduced unnecessary administration, increased regulatory burdens, lacked clarity in some aspects, and allowed Member States to introduce additional requirements which limited harmonization, resulting in delays and increased costs for researchers.

Shifts in clinical trial application (CTA) rates over time indicate if the attractiveness of a country or region for the conduct of clinical trials is growing or decreasing (Hartmann, 2012). The number of clinical trials conducted in the European Union fell by 25 per cent between 2007 and 2011. There has been a decline in CTA rates in the Netherlands, Germany, France and the UK (1.9%, 2.3%, 3.1% and 5.3% average annual decreases). In part this decrease can be attributed to the Directive-driven policies bringing about a change from the more liberal policy environments to more red-tape processes of trial authorisation. Southern European countries like Italy and Spain benefited to some extent from policy changes in the Directive, and since 2001, the number of CTAs in Italy

and Spain increased significantly (5.0% and 2.5% average annual growth). Some European countries have developed best practices, which a new European legislation should take into consideration (Hartmann, 2012).

Potential Solutions in the New Regulation

On 17 July 2012, the European Commission adopted and published its proposal for a new Regulation for revising the EU rules on clinical trials. The European Commission believes that the new proposal has the potential to create a more favourable environment for the conduct of clinical trials in the European Union. It is intended that the revised rules will ensure that the EU remains an attractive location for clinical research – which is of vital importance for Europe's competitiveness and innovation capacity. This new Regulation is planned to come into force in 2014.

A Regulation unlike a Directive takes direct effect in all EU Member States, does not have to be imposed into national law and supersedes existing legislation. It is proposed that it will introduce some significant measures that will contribute to boost clinical research in Europe, for example:

- A streamlined application procedure via a single entry point - an EU portal and database, for all clinical trials conducted in Europe. Registration via the portal will be a prerequisite for the assessment of any application;
- A single authorisation procedure for all clinical trials, allowing a faster and thorough assessment of an application by all Member States concerned, and ensuring one single assessment outcome and authorisation per Member State;
- The extension of the tacit agreement principle to the whole authorisation process which will give sponsors and researchers, in particular small and medium enterprises (SMEs) and academics, more legal certainty;
- Improved conditions for conducting multinational clinical trials, which are key for rare and serious diseases;
- Strengthened rules on the protection of patients including a more efficient facility for reporting untoward events and improvement of informed consent via establishing a responsibility on the researcher to provide a risk benefit analysis on patient information forms;
- More transparency on the conduct and results of the clinical trial, through

the compulsory prior registration on the EU portal;

- The possibilities for the Commission to conduct controls in Member States and third countries to ensure the rules are being properly supervised and enforced.

Data Protection Legislation

All countries have Personal Data Protection legislation and all research studies must comply with this law. These laws generally deal with participants' privacy, prior informed consent, processing of personal data etc. Within Europe these laws are based on interpretation of the European Data Protection Directive (95/46/EC). In January 2012, the European Commission published a draft Data Protection Regulation with a view to replacing the existing Data Protection Directive and associated Member State legislation. The Regulation is now being considered and amended by the European Parliament and Council before it is adopted. This process may take until 2015. The Data Protection Regulation covers the use of personal data across a wide range of sectors and will affect how patient data are used in research. Provisions in the original text of the Data Protection Regulation were made to support research. In March 2014 however, the European Parliament adopted amendments that would severely restrict the use of any personal data for scientific research purposes without specific consent. Understandably this Regulation is proving controversial within the research community across Europe. A co-ordinated response from Research groups across Europe has been instigated to ensure the research concerns are considered.

Implications for recruitment and consent in the new legislations

If the new Data Protection Regulation is adopted as currently proposed this will have very significant implication for all research including observational and database research, which will in future only be permitted if explicit consent has been gained even when data has been pseudonymised. The proposals however allow that Member States could pass a law permitting the use of pseudonymised data concerning health without consent, but only in cases of "exceptionally high public interest" and with authorisation of the competent supervisory authority. The amendments would introduce a requirement for a competent supervisory authority to authorize processing. This authorisation from a competent

supervisory authority will add further bureaucracy and potential for delays.

Similarly although the Clinical Trials Regulation sets out in some detail the form of consent required in the clinical trial context and provides for consent by simplified means, in certain cases the Clinical Trials Regulation also makes it clear that its provisions are subject to the EU Data Protection Directive; and therefore, there is still potential for inconsistencies and confusion to arise as to what is required for valid consent under the Clinical Trials Regulation, and whether this is valid consent under the proposed EU Data Protection Regulation.

Data Transparency and IP issues in the new EU Clinical Trials Regulation

Currently, pharmaceutical companies do not have to publish all clinical trial data concerning their products. It is estimated that only half of all clinical trials have been published in academic journals, meaning that not all data showing negative results or possible harmful effects of medicines is being made publicly available. The amendments in the new EU Clinical Trials Regulation include new requirements for public transparency of clinical trial results (data) collected from clinical trials performed in the EU 'in order to have safer medicines and therefore safer prescribing'.

Pharmaceutical companies and academic researchers therefore will be required to publish the results of all their approved European clinical trials. Detailed summaries of clinical trial data relating to medicinal products, including a plain-language summary, will have to be posted in a publicly-accessible, free and searchable EU database one year after the termination of the trial (e.g., last visit by the last subject or as otherwise defined in the protocol). On the same database, within 30 days of the marketing application's authorization, rejection or withdrawal, sponsors will be required to post the full clinical study reports (comprehensive information on each study) that were submitted to the European Medicines Agency (EMA) in support of the marketing application. Failure to post the summaries or final clinical study reports will result in fines.

There are positive benefits, but also potentially negative consequences of this new requirement for more transparency and sharing of clinical trials data:

The new rules are aimed to enhance cross-border cooperation and increase operational efficiencies in conducting larger clinical trials with more viable and

more reliable results. By optimizing the surveillance of drug safety and effectiveness, as well as increasing the accuracy of research reports on the benefits and risks of drugs, the regulation aims to accelerate innovation and make the EU more competitive and attractive for clinical studies. It also provides a framework for further inquiries and research into existing data. In addition, such databases would allow public individuals and advocacy groups to gain more information about their specific medical problem. Also, importantly, (if combined with effective safeguards for research participants' safety), the new regulation may increase public confidence in medical research and pharmaceuticals.

However, increased transparency and sharing of all data could also result in negative consequences. Compulsory disclosure of clinical trial data may for example impact the patentability of products and processes. This could adversely affect incentives to invest in research and to develop new drugs in Europe. Other concerns relate to the risks for the privacy-protection of research participants, and to the problem that the new transparency might encourage market competitors or unskilled analysts to independently publish poorly conducted analyses. This highlights the complexities around operation and administration of the new trials data sharing system.

Currently the data disclosure requirements will not apply to retrospective trials and therefore data for medicines that are currently in use. Additionally, clinical trial data that is not submitted for marketing authorisation will not need to be published in full. Although the regulation states that clinical trial data cannot be considered commercially confidential, this provision is not legally binding. The European Federation of Pharmaceutical Industries and Associations (EFPIA) is proposing that clinical trial data should fall under the definition of a 'trade secret' within the EU's upcoming directive on the protection of trade secrets. In addition, the industry is lobbying the EU and US government for a harmonised, restrictive approach on clinical trial data disclosure to protect commercial interests.

The Clinical Trials Regulation will not be enforced until six months after a new EU portal for the submission of data on clinical trials and the database have become fully functional. The EU portal is currently being developed by the EMA, and this is expected to take at least two years. Hence, the Regulation is expected

to apply in 2016 at the earliest (with an opt-out choice available until 2018).

Research Ethics Committees in the European Member States

According to the current EU Directive, a research ethics committee (REC) is 'an independent body in a member state, consisting of healthcare professionals and non-medical members, whose responsibility is to protect the rights, safety and wellbeing of human subjects involved in a clinical trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the clinical trial protocol, the suitability of the investigators involved in the trial and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent'.

Currently, in EU countries both a national competent authority and a REC evaluate and approve the same clinical trial application. However, the procedures for obtaining ethical approval varies widely; from submission and approval required for each site, to approval from a lead or national committee serving as approval for all participating sites in the country, lead ethics approval from a central site with confirmatory approval at the other sites, and national ethics approval followed by additional submission and approval from the local ethics committees. A good summary of the current challenges for obtaining approvals to conduct a multi-country trial is provided in the article by Schnitzbauer *et al* (1990). For their trial involving 10 European countries (Austria, Belgium, Finland, France, Germany, Italy, the Netherlands, Spain, Sweden, and the United Kingdom) with a total of 40 sites in the EU, approvals had to be obtained from a total of 38 national and local ethics committees in the 10 countries.

While a review requires both ethical and scientific aspects to be evaluated, the current system can lead to unnecessary bureaucracy, communication failures and unclear procedures and accountability between the competent authority and the REC. The regulation of RECs is the responsibility of member states and consequently RECs vary widely across Europe. For example, REC membership varies from 50% lay members in Denmark to a group of multidisciplinary clinical scientists with only one lay member in the Netherlands. There is also a very different number of RECs present in member states, which is not related to population size or research output (**Table** 2).

Table 2: Research output and number of ethics committees in EU member states since 2006 using data from Web of Science*

EU Member State	Number of RECs	Research output (Output per member state divided by number of inhabitants)	Research output per 1000 inhabitants
Latvia	5	116	0.05
Romania	1	1,430	0.07
Bulgaria	103	780	0.10
Cyprus	3	180	0.21
Malta	1	101	0.25
Slovakia	80	1510	0.28
Lithuania	3	1,138	0.33
Poland	52	13,020	0.34
Estonia	2	481	0.37
Portugal	1	4,282	0.40
Luxembourg	1	197	0.42
Hungary	1	4,264	0.42
Czech Republic	109	5,406	0.53
Spain	136	43,530	0.95
France	40	62,597	0.96
Slovenia	1	2,128	1.06
Italy	264	68,311	1.13
Germany	53	93,526	1.14
Greece	1	15,266	1.31
Ireland	13	6,133	1.38
Austria	26	11,925	1.41
Belgium	215	15,848	1.50
UK	114	112,879	1.82
Finland	25	9,971	1.86
Sweden	7	21,380	2.28
Denmark	8	12,724	2.29
Netherlands (27 RECs and a central committee)	28	40,189	2.43

*adapted from Kenter and Cohen (2012)

There is also a lack of transparency and no systematic evaluation of the quality of competent authorities and RECs, and this results in little assurance about the expertise of the reviewers. Only the Netherlands has a centralised approval procedure for candidate REC members that involve evaluation of their expertise and experience.

With the new Clinical Trials Regulation, the EU aim for a harmonisation of RECs across Europe, including the time taken for trial review and the issues that a committee should take into account. However, for the assessment of drug trials,

centralisation would prove difficult due to the broad scope of proposals and assessment issues. The required expertise necessitates knowledge from local authorities, academic centres of excellence, and other experts and to maintain such expertise in one central organisation would be challenging.

Kenter and Cohen (2012) suggest how the current two-tier assessment system could be replaced by one integrated assessment and propose the establishment of a transparent quality and accreditation system for RECs in the EU. They propose that the foundation of a Health Research Authority (HRA) in every member state, as proposed for the UK, might facilitate this process so that all studies with human participants (and not only drug trials) are reviewed by competent RECs using the expertise of the full academic medical community. In the Netherlands one central body, the Central Committee on Research Involving Human Subjects (CCMO) is involved in the accreditation and oversight of RECs. This CCMO could serve as a good example of such a HRA and may facilitate the establishment of a trans-national network of experts, as the availability of scientific expertise for review is likely unevenly distributed within the EU. The authors propose that only after all this has been established can a single whole EU approval of an international health research application be considered.

Introduction: methods and data

The time frame for this WP1 Initial Rapid EARL Report (Task 1.1a) was four months from the launch of PREPARE. The teams in Dublin (UCD) and Cardiff (CU) held weekly local project team meetings. In addition weekly teleconference (TC) meetings were conducted between Dublin and Cardiff.

For WP1, the research methods employed a multi-strand approach. The initial phase consisted of scoping existing key academic and secondary literature in a variety of related EARL areas of interest. This provided the basis for the detailed demographic and more specific country as well as thematic information that formed the basis for the qualitative interview guide. The approach directed the scope of the research package and established a dynamic detailed research protocol that informed a) the more specific literature search, b) a survey and c) a series of qualitative in-depth interviews conducted face-to-face and by telephone.

Mapping of existing EARL practices was completed through literature searches and consultation of publicly available documents. Information gathered was used to populate a template for each European Country. Complementary data regarding research in epidemics/pandemics and pre-approval processes was reviewed and included. The information was triangulated within and between different data sources (Primary and Secondary).

Each research activity will now be described together with its aims, methodology and key findings, strengths and limitations.

Aims: To collect and collate information from all EU countries, to act as a resource and to provide a baseline of current available information.

COUNTRY DATA

Methodology

Data Collection

Information on the research governance requirements and application processes required for research studies (clinical trial and observational) in each EU country (table 3) was collected from relevant websites. At the first stage of the data collection, the public health authority, the competent authority and the ethical committees of each country were identified. In almost all countries the official agencies have websites available either in local language, in English language or in both. In many countries the application and approval process of research studies and ethical approval procedure was described in detail on the websites of the competent authority and the ethics committees. In that case the information was directly taken from the website/document and the links to the original sources were given. In some countries the information was not readily available on the websites of the competent authority or the ethics committees; for those countries the national legislations regulating clinical trials were referred to for obtaining the details on application and approval process. Wherever the information was only available in the local language, a translation to English was not attempted; instead a direct link to the website/document in the original language is provided.

Data collected through the online survey among European experts in clinical trials and members of the European Clinical Research Infrastructure Network (ECRIN) network were also used to complement the information collected from the websites of national agencies. Information was also obtained from the following sources, European Forum for Good Clinical Practice (EFGCP website); Report on "The Procedure for the Ethical Review of Protocols for Clinical Research Projects in Europe and Beyond"; the WHO's "Health Systems in Transition". Information was also obtained from the European Network of Research Ethics Committees (EUREC), and the Translational Research in Europe – Assessment and Treatment of Neuromuscular Diseases (TREAT-NMD) Regulatory Affairs Database.

Table 3 : EU member states (n=27) and associated countries (n=14)

EU Member States

Austria	Germany	Netherlands
Belgium	Greece	Poland
Bulgaria	Hungary	Portugal
Cyprus	Ireland	Romania
Czech Republic	Italy	Slovakia
Denmark	Latvia	Slovenia
Estonia	Lithuania	Spain
Finland	Luxembourg	Sweden
France	Malta	United Kingdom

The EU Associated Countries

Albania	Liechtenstein
Bosnia and Herzegovina	Moldova
Croatia	Montenegro
FYR Macedonia	Norway
Faroe Islands	Serbia
Iceland	Switzerland
Israel	Turkey

The information compiled for each country report, included:

- Country Demographics and Map
- Time zone
- Language
- Basic Introduction to Health Care System
- Ethics Committee Configuration
- Application, approval process
- Additional requirements for vulnerable participants
- Application time lines, contact details, web page addresses
- Fees (if applicable)
- Regulatory Authority contact details
- Biological Sample Requirements
- Investigational Medicinal Product Requirements
- National data protection legislation
- Reporting Obligations
- Behavioural and Cultural Issues
- Presence of PREPARE clinical networks
- Fast-track approval processes during epidemics/pandemics
- Perceived barriers to conducting research during a pandemic/epidemic
- References

The country reports are outlined in the **Appendix.**

Findings and Discussion

Health care system

Health care systems in the EU countries are generally funded by the government or by compulsory individual contribution. In most countries primary care clinical practitioners act as gatekeeper to the secondary care system. Secondary and tertiary cares are provided by hospitals owned publically or privately. Public hospitals are owned by central government or local government/municipalities. Each country has a separate public health agency for health protection, promotion and disease surveillance. Website addresses and contact details of public health agencies are given in the country reports.

Application process of clinical trial approval

Following the EU Clinical Trials Directive 2001/20/EC, each country has a Competent Authority (CA) to authorise clinical trials in that country. Names, website addresses, and contact details of CAs in each country are provided in the Country Report. All countries follow the application procedure described in the European Commission's, detailed guidance on the request to the competent authorities for authorisation of a clinical trial for an investigational medicinal product (IMP) for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1, 2010/C 82/01)' for clinical trial authorisation. The time line of approval process ranges from 15 days to 90 days and in most of the countries it is 60 days. The CAs usually charges fees for trial approval application, but in many countries fees are waived for non-commercial studies.

Details of application process and approval procedures are clearly described on the websites of most of the CAs. However, no information or very limited information is available on the website of the CAs in France, Greece, Romania, and Slovakia. In some of the countries detailed information is available only in the local language and not in English; Bulgaria, Germany, Lithuania, Poland, and Portugal are examples. No information was found on fast-track approval and pre-approval of protocols or process of fast-track approval during epidemics/pandemics for any country.

Structure of ethics committees and application/approval process

In all countries approvals from relevant Research Ethics Committees (RECs) is a prerequisite for starting a clinical trial. The application to the REC can be submitted prior to, or, simultaneously with the application to the competent authority. Out of the total 27 EU member states, ethics committees of 18 countries have given a link to an ethics application form on their websites. In Hungary no separate application is required to the REC; instead the CA forwards a copy of the application for REC opinion. There are different time-frames in different countries for different kinds of trials, so, for example in the UK, genetic or stem cell research involving medicinal products with genetically modified organisms might take up to 90 days, whereas a 60 day limit is set for others.

The time line for ethical approval ranges from 15 days to 90 days and in most of the countries it is 60 days. In the majority of the countries RECs charge fees

for initial applications and amendments, which typically ranges from a couple of hundred euros to thousands. However, in France, Slovenia and UK there are no fees for REC applications and in some countries like Hungary ethical review is free of charge for non-commercial studies.

Analysis shows that there are substantial variations in the structure of ethics committees and application/approval processes between countries. Central RECs responsible for authorising clinical trials only exist in Cyprus, Hungary, Luxembourg, and Malta. Whereas, in Greece, Portugal and Slovenia, though local ethics committees exist, a central Ethical Committee assumes responsibility to review Clinical Trials of Medicinal Products for Human use. In most of the other countries there is a central REC in addition to RECs at regional or local level.

Pre-approval / fast-track approval / data protection

Information regarding fast track research approval is not available on the websites of CAs or RECs of any country. No information could be found on pre-approval of study protocols or waived consent for any country. Results from our online survey (see survey section and appendix) / interviews suggest that France, Greece, Slovenia, the UK and Ireland have some provisions to expedite review.

Following the EU Directive 2001/20/EC, almost all countries have implemented special requirements for studies involving children or vulnerable populations. These generally include consent from parents/guardian or a legal representative.

In studies including collection and use of human tissues, special requirements are needed only in Denmark and the UK. For all countries no clear information could be found on regulations regarding bio-banking, and transportation and sharing of samples. Although they are required to conform to the EU Tissue and Cells Directive via the Human Tissue (Quality and Safety for Human Application) Regulations 2007.

The European Union Tissue and Cells Directives: The European Union Tissue and Cells Directives (EUTCD) set out to establish a harmonised approach to the regulation of tissues and cells across Europe. The Directives set a benchmark for the standards that must be met when carrying out any activity involving tissues and cells for human application (patient treatment). The

Directives also require that systems are put in place to ensure that all tissues and cells used in human application are traceable from donor to recipient.

Links to each country's data protection law is given in the country reports.

Overall EU Map Assessment Red/Green/Yellow

- For each PREPARE WP
- Current map of activities
- Identified risks and solutions
- Potential opportunities

SURVEY

Aims

The aims of the survey were to collect the views of key informants in research networks across many European Union member states and associated countries on:

- Research approval processes (including names of organisations providing approval, costs, time frames, etc.)
- Factors that are likely to cause delays in obtaining approvals or conducting research in a pandemic situation
- Procedures for obtaining pre-approval prior to a pandemic / epidemic or fast track approval during a pandemic / epidemic.

Methodology

Data Collection

The research team developed a survey (see Appendix 3) based on the aims of PREPARE and information gathered through interviews with PREPARE partners in Antwerp (PREPARE launch meeting). The survey comprised primarily of yes/no questions, often followed by an open question to allow respondents to provide more detailed 'free text' or qualitative responses. It included questions on the factual EARL processes in addition to questions targeted at collecting impressions and perceptions of the processes. One question asked respondents to rank a series of factors that might impact on setting up a study during a pandemic, from the most challenging to the least challenging. Finally, key PREPARE partners were invited to comment on and pilot the draft questionnaire. This resulted in a number of revisions.

A data collection website was created and the survey launched through the PREPARE WP8 CRISP platform.

The final survey was disseminated to the associated PREPARE networks for completion. These networks included the GRACE/TRACE Primary Care Network, Hospital Networks (EU IMI COMBACTE and CAPNETZ, the European Society of Intensive Care Medicine (ESICM) and the paediatric infectious disease

clinical trial network (PENTA-ID)). The survey was additionally distributed to the European Clinical Infrastructures Network (ECRIN) whose members include administrative experts on regulatory and ethical requirements and adaptation to local contexts.

Data were collected between 23/04/2014 and 01/062014

Analysis

Survey responses were first separated by country and information used to corroborate and supplement findings that had been incorporated into the country documents. Responses to binary (yes / no) responses were summarised by presenting the number and proportion as a percentage. Respondents were asked to identify a time range in which survey approvals were obtained. These time ranges were identified for each country. Where a number of survey responses were collected for a single country, the full range of responses was represented.

Data from the question that asked respondents to rank factors presenting a challenge to study set up during a pandemic/ epidemic was found not to contain only ranked scores (51 % of respondents had included one or more ranked scores more than once).

Therefore the data were analysed in two groups: i) those that ranked the responses and ii) those that gave each response a rating. SPSS was used in the quantitative analyses.

Survey findings

Description of the Sample

Number of respondents: A total of 56 responses were received. There were 43 responses from EU member states and 13 from EU associated countries. The number of survey responses received per country varied from 4 (France, Spain) to 0 (Belgium, Bulgaria, Cyprus, Malta, Slovakia, Sweden) (see table 4).

Table 4: Number of survey responses received per country

Responses	EU member states	EU Associated countries
0	Belgium, Bulgaria, Cyprus, Malta, Slovakia, Sweden	
1	Austria, Czech Republic, Finland, Greece, Latvia, Lithuania, Romania, UK	Croatia, Kosovo, Norway, Republic of Moldova, Serbia
2	Denmark, Estonia, Ireland, Luxembourg, Netherlands, Poland	Albania, Bosnia and Herzegovina, Switzerland, Turkey
3	Germany, Hungary, Italy, Portugal, Slovenia	
4	France, Spain	

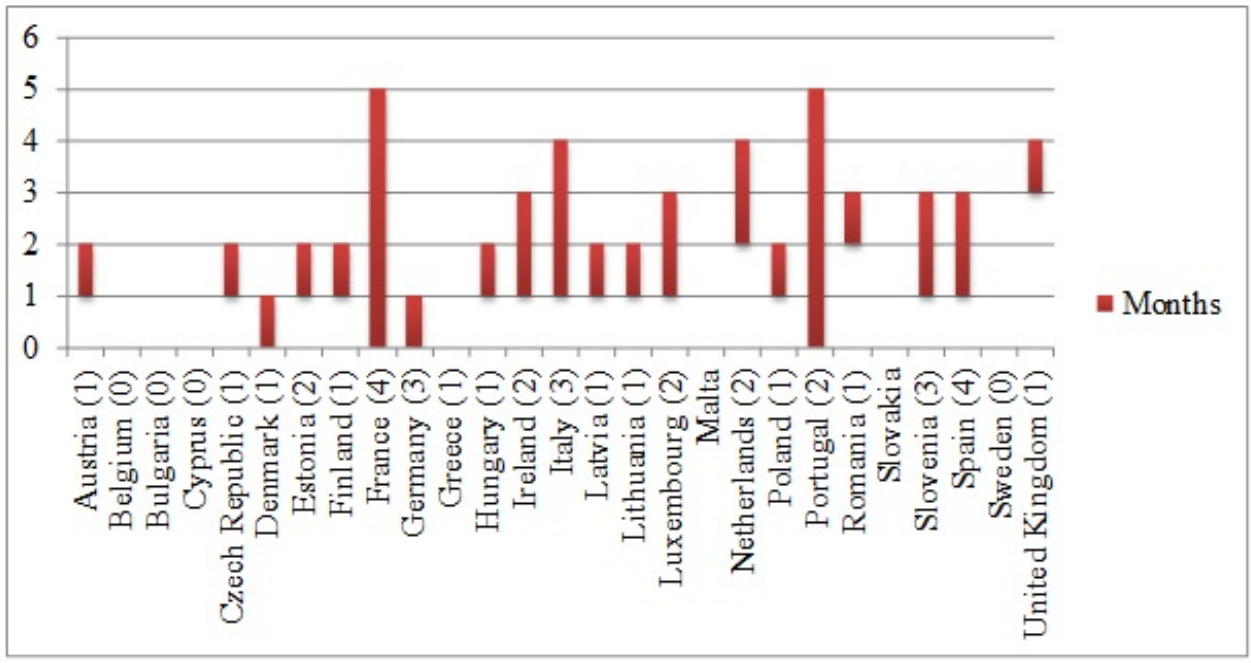
Timelines for approvals

Participant responses (n=45) on timelines for approvals in EU-member states are presented in Figures 1 and 2 below. In the majority of these countries, ethical and Investigational Medicinal Product (IMP) approvals may be obtained within 3 months. There was more information available from participants about these timeframes with regard to ethical approvals than for IMP approvals.

Ethical approvals (see figure 1):

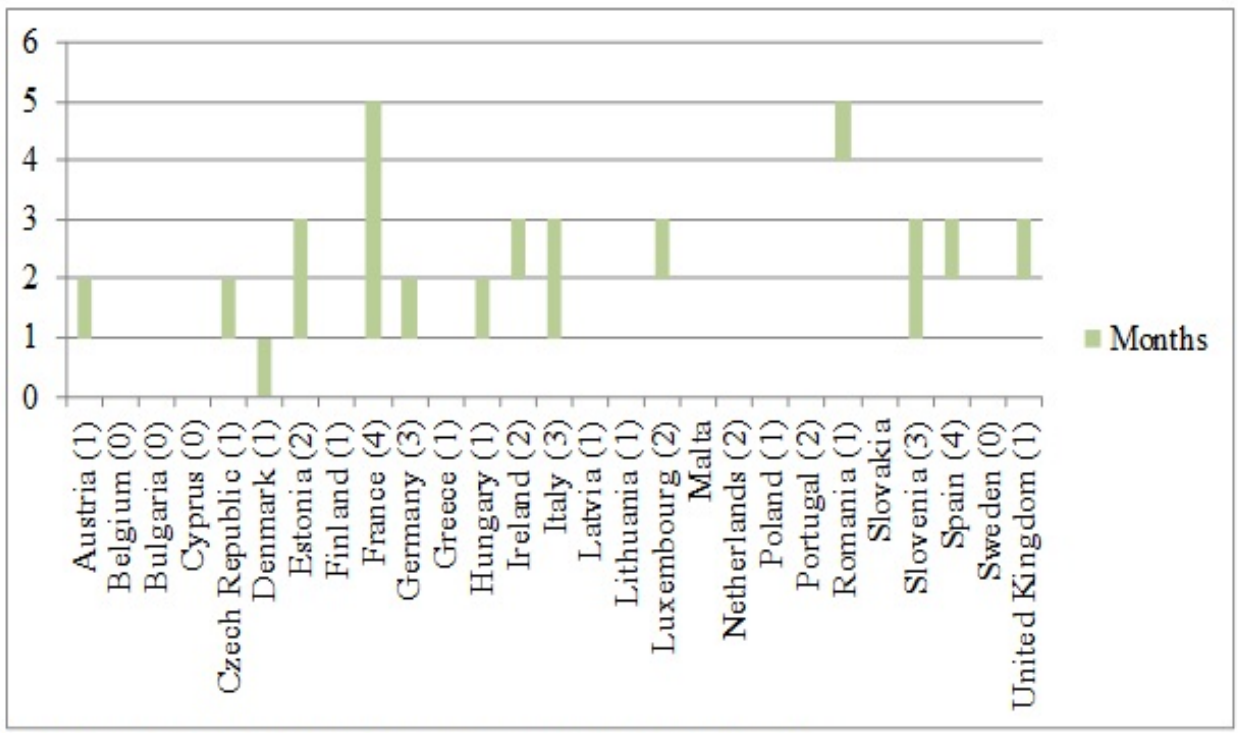
- Most respondents (n=41) answered this question;
- In two countries, ethical approvals may be obtained within a month (Denmark, Germany);
- In most countries approvals are obtained within a one or two month window. In two countries (France, Portugal) there was greater variability in the amount of time required to obtain ethical approvals.

Figure 1: Timeframe for ethical approvals for EU member states (n=38)*



* where timeframes = 5 months, this suggests approvals may take > 4months

Figure 2: Timeframes for approvals from medicines regulators for EU member states (n=38)*



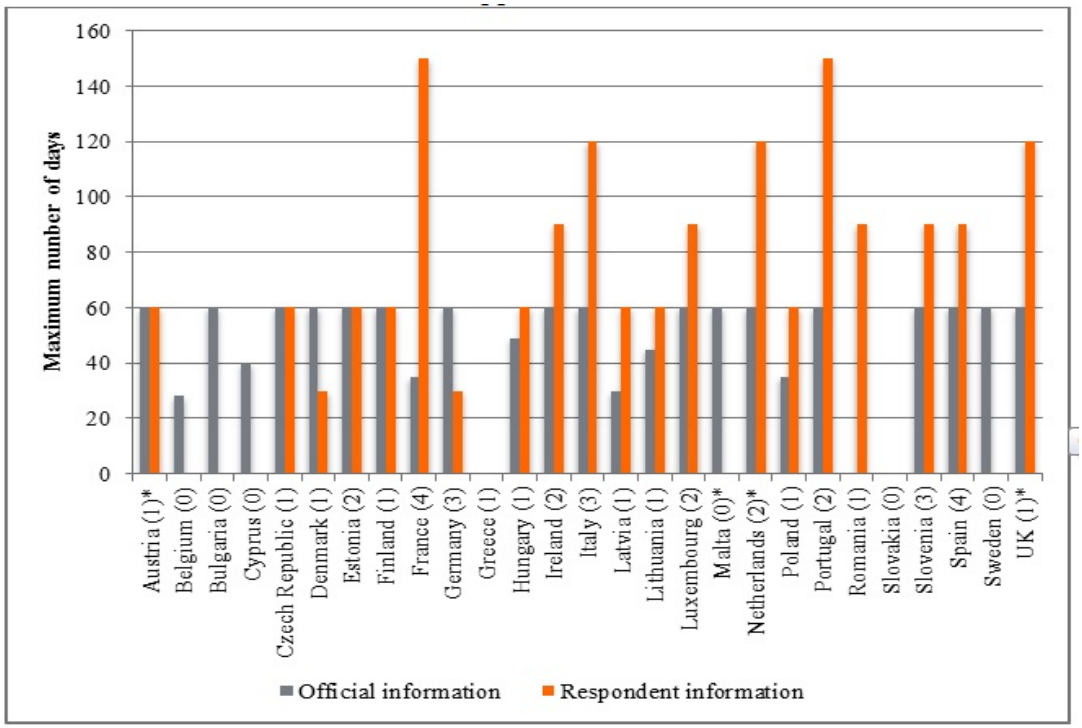
* where timeframes =5 months, this suggests approvals may take > 4months

Investigational Medicinal Product (IMP) approvals (see fig 2):

- There was less information about timelines from survey respondents (n=27 responses, 18 non responders, or response indicated "don't know").
- Also there was less variability in the time frames, with most responses suggesting a one-month window (n=9). France has the greatest variability (from 1 to > 4 months).
- In Romania IMP approvals take more than 4 months.

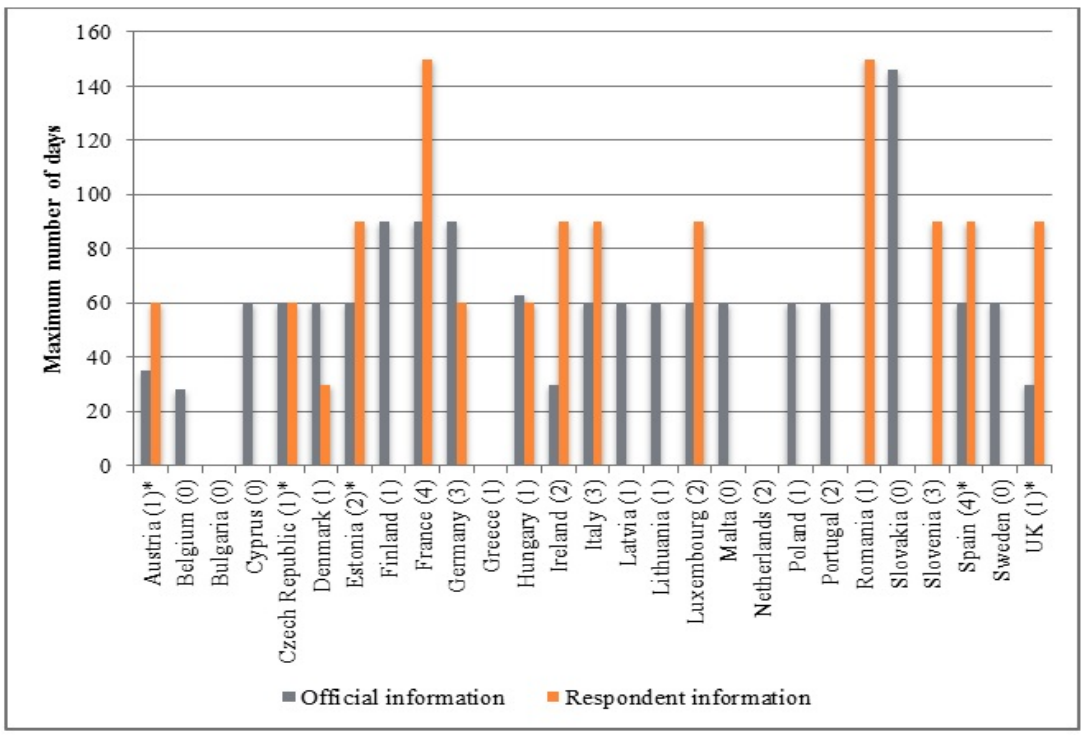
Survey respondent's perceptions of the actual time taken to obtain approvals from ethics committees and medicines regulators were compared with the timeframes published by regulatory bodies on their websites as the guide or standard to which they operate. These are presented in figures 3 and 4 (for EU member states) and illustrate the discrepancy in a number of countries between respondent experience and timeframes given. These discrepancies may arise when committees are considering an application and "stop the clock" or they may represent other kinds of delays. The experience of respondents from Germany and Denmark suggest efficient processes and rapid approvals. These findings should be interpreted with caution, however as we had only a small number of respondents from each country (between 0 and 4).

Figure 3: Comparison between official information and respondent experience of timeframes for ethics approvals in EU member states*



*A 90day limit is set in these countries for studies involving stem cell, gene therapy or medicines with genetically modified organisms

Figure 4: Comparison between official information and respondent experience of timeframes for IMP approvals in EU member states*



*A 90day limit is set in these countries for studies involving stem cell, gene therapy or medicines with genetically modified organisms

Research Ethical Committee (REC) approvals for different study designs

Of the 56 respondents, 46 (82%) indicated if REC approval processes in their country were different for observational or qualitative research compared with experimental research, such as clinical trials (table 5).

Table 5: Countries for which observational or qualitative research approval processes differ or are the same as those for experimental studies such as clinical trials

	EU member states	EU Associated countries
Process not the same	France, Greece, Latvia, Netherlands, Portugal	
Process is the same	Austria, Czech Republic, Estonia, Finland, Hungary, Ireland, Italy, Lithuania, Luxembourg, Romania, Slovenia, UK	Bosnia and Herzegovina, Croatia, Kosovo, Norway, Switzerland, Turkey
Don't know	Denmark, Germany, Poland, Spain	Albania, Republic of Moldova, Serbia

- Information about 22 of the 27 EU member states was available from the survey responses.
- In countries where the approvals processes were different for observational or qualitative research (France, Greece, Latvia, Netherlands, Portugal and Spain), these were described as simpler, quicker and easier than obtaining approvals for clinical trials.
- Respondents for Germany gave contradictory responses. One said the processes for obtaining ethical approvals was the same; while the other said the requirements for observational and qualitative research in general were not as high and described a different process that might be followed. Two respondents from Poland also gave contradictory responses with one indicating that insurance requirements may be different for observational or qualitative research. Respondents from Spain also disagreed. Consequently these countries have been placed in the "don't know" category above until this information can be verified.

When asked about factors that might make obtaining approvals more difficult, most respondents did not answer the question or indicated they didn't know

and/ or weren't aware of any factors (n=45, 80.4%). Of the 11 respondents (19.6%), the following factors were identified:

- Studies with vulnerable populations such as paediatrics (Hungary, Italy, Latvia, Poland, Portugal)
- Studies involving genetics or stem cells (Estonia, Latvia, Spain)
- Certain study designs such as cluster RCTs where waived consent may be required (Netherlands), or adaptive trials of which ethics committees may have little experience (Germany)

Challenges to setting up a research study

Participants were asked to rank 11 factors that may present a challenge to the setup of a study during a pandemic or epidemic. Of the 56 respondents, 19 (33.9%) did not complete this question. Non-respondents were from a range of countries. Of the 37 (66.1%) respondents who answered the question, 18 (48.6%) ranked the factors while 19 (51.4%) did not rank the questions. Those who did not rank the questions most likely assigned an importance rating to them. Consequently the data were analysed in two groupings according to the way participants responded to the question. Data are presented in table 6.

Table 6: Median and interquartile range (IQR) for each factor identified as presenting a challenge to study set up during a pandemic or epidemic, for ranked and non-ranked data

Factor	Ranked Scores Median (IQR)	Rated scores Median (IQR)
Clinical staff too busy	2.0 (1.00-4.25)	3.0 (2.00-7.00)
Consent	5.0 (3.75-6.50)	6.0 (4.00-9.00)
Contracting	4.5 (1.75-7.00)	8.0 (4.00-9.00)
Recruiting research sites	5.0 (3.00- 6.25)	7.0 (3.00-9.00)
Supply of IMP/ placebo	7.0 (4.00-9.00)	4.0 (3.00-6.00)
Timely identification of participants	4.5 (2.00-6.25)	5.0 (3.00-8.00)
Training sites	7.0 (4.00-8.25)	7.0 (3.00-9.00)
Participant recruitment	5.0 (2.50-7.25)	6.0 (3.00-8.00)
Storage of samples	9.0 (8.50-11.00)	8.0 (4.00- 10.00)
Sponsor's research department protocol	8.0 (5.00-10.00)	6.0 (3.00-9.00)
Transport of samples	10.0 (8.00-10.00)	5.50 (3.00-9.50)

Frequency distributions for the ranked data are presented in figures 5 and 6. These data present the relative importance of each factor when factors are compared with each other. Frequency distributions for non-ranked data are presented in table 6. These data present participant perspectives of the importance of each factor in presenting a challenge to study set up, on a scale of 1-11.

Where participants ranked the factors (table 6, figure 5) data suggest:

- 'Clinical staff too busy' is the most important factor – 8 respondents (44.4%) gave it the highest ranking. Of the respondents, two thirds (n=12, 66.7%) allocated a ranking of between 1 and 3. (See the frequency distribution that clusters toward the left). In addition, from table 6, the median for this factor is the highest.
- Respondents allocated a ranking of between 9 and 11 to sample storage (n=13, 72.2%) and transport of samples (n=12, 66.7%), suggesting that these are the lowest ranking factors (see frequency distribution clustered toward the right). The median for these factors is also the lowest at 9.0 and 10.0 respectively (table 6). This may suggest that infrastructures are in place to conduct research of this kind.
- The distribution for contracting suggests discrepancy in the responses with some participants considering it to be an important challenge (n=4, 22.2% allocated a 1), while other respondents ranked it lower (n=4, 22.2% ranked 7). This may reflect differences across countries, but also may represent differences in interpretation of what contracting might involve.
- Also, the distribution of supply of IMP/placebo seems to be considered a relatively low challenge to study set up, as 8 respondents (44.4%) ranked it on the lower end of the scale (between 8 and 11).

Figure 5: Frequency distributions for factors identified as a challenge to study set up where participants did rank responses (n=18)

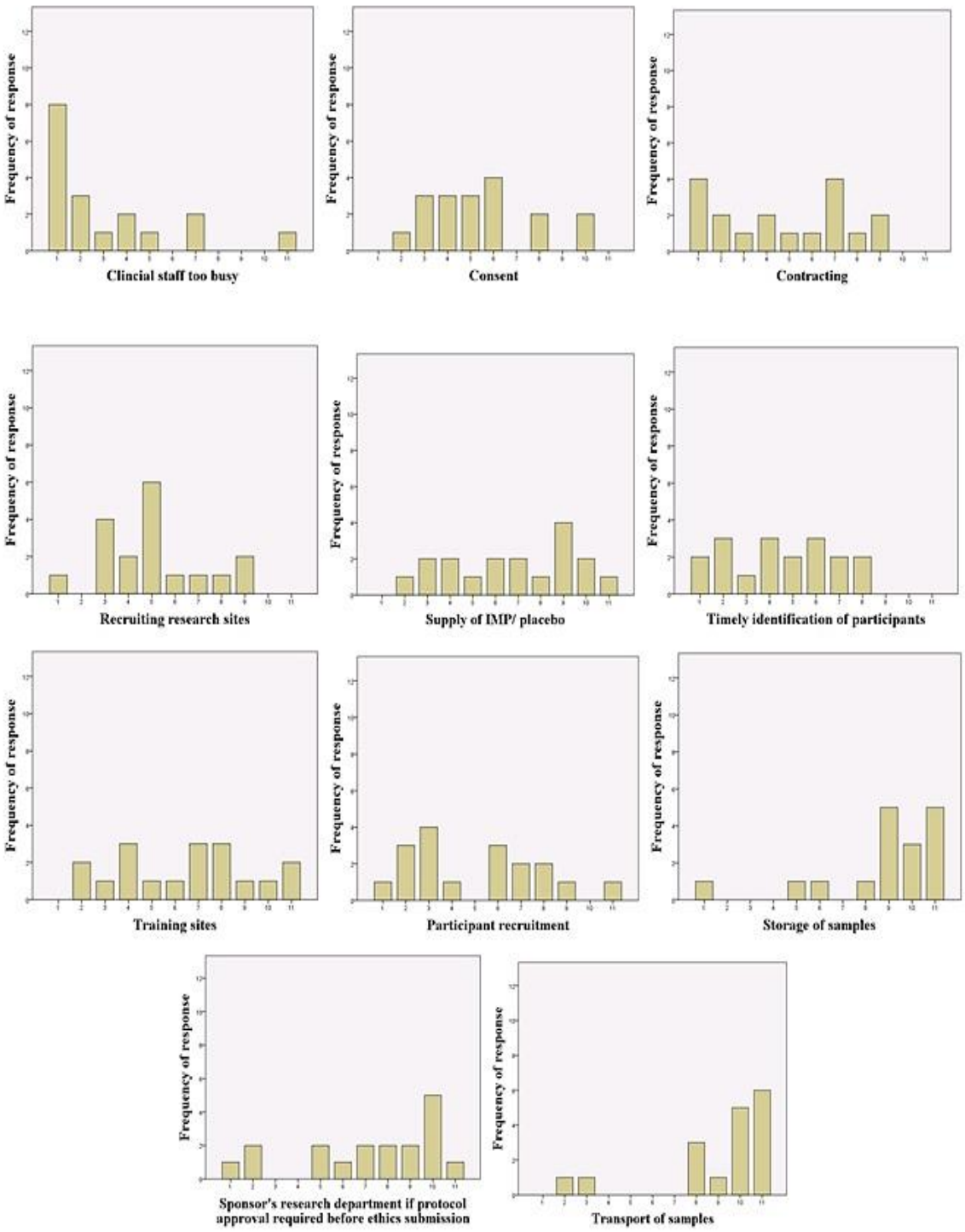
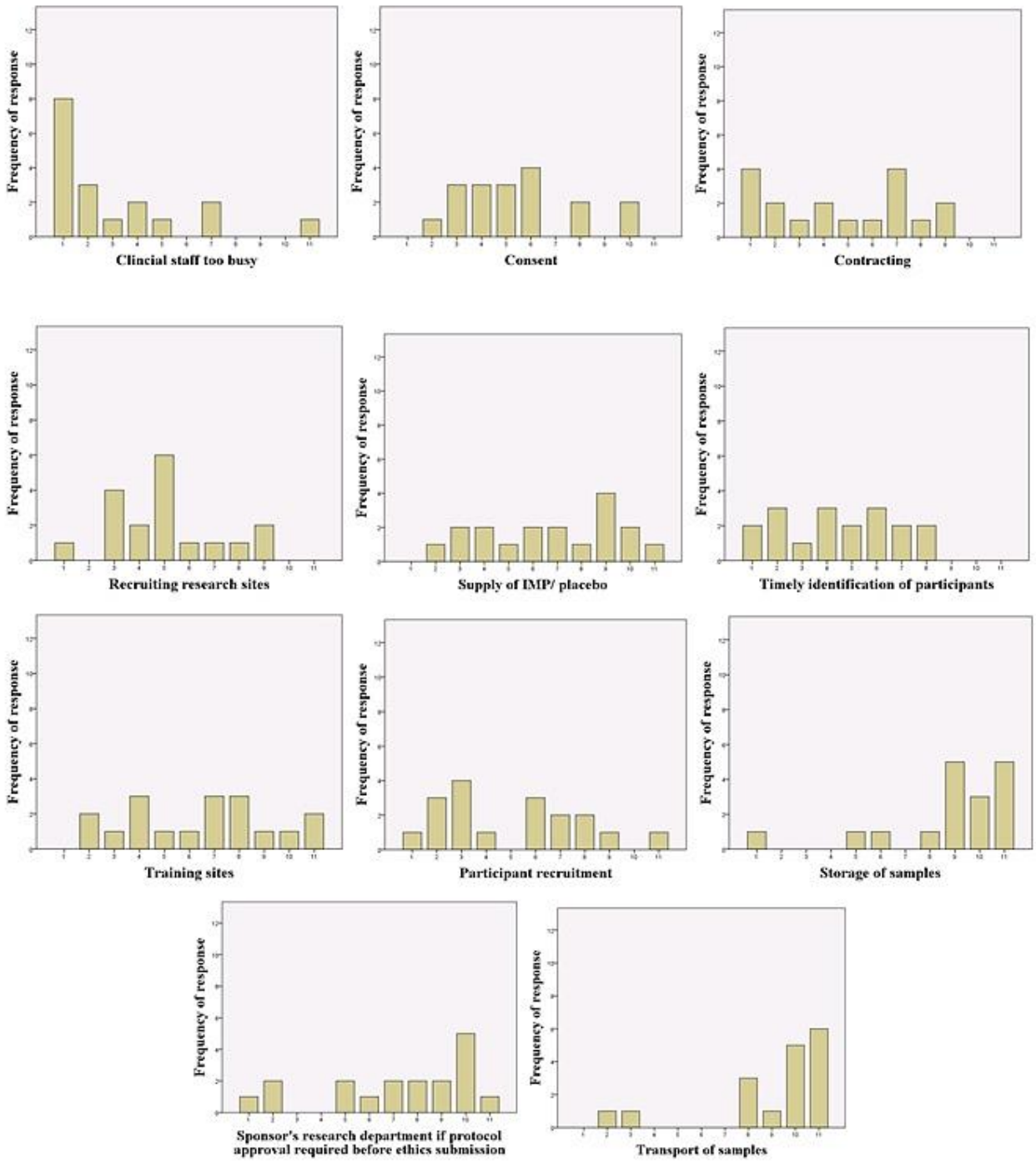


Figure 6: Frequency distributions for factors identified as a challenge to study set up where participants did not rank responses and chose a level of importance (n=19)



Where participants did not rank responses and allocated a number between 1 and 11 (table 6, figure 7):

- These data should be interpreted with caution, as respondents were not replying directly to the question asked of them.
- Again, clinical staff being too busy was considered a key challenge to study set up during an epidemic or pandemic with two thirds (n=13, 68.4%) of participants allocating a score of between 1 and 3. The median for this factor was also the highest in this data set (median =3). This finding is consistent with that using the ranked responses data (table 6).
- These data also suggest that sample storage may not present a particularly important challenge to study set up, with 14 (73.7%) respondents allocating a number on the lower end of the scale between 8 and 11. Again this is consistent with the ranked response data (table 6). The median for this factor was the lowest in the data set (median = 8), together with contracting, with the IQR located at the end of the scale. However using these data, the responses about whether transport of samples may present a challenge, are inconclusive (distribution relatively flat). The median for this factor was mid – scale (median = 5.5) with a wide IQR suggesting variability across countries (table 6).
- Contracting was not indicated as a particularly important challenge to study set up with 10 respondents (52.6%) allocating a number between 8 and 11. Compared with the rank response data (table 6), these data suggest that contracting may not necessarily present a challenge to study set up.
- Contrary to what was observed using the ranked response data (table 6), these data suggest that supply of IMP/ placebo may present an important challenge to study set up during an epidemic/ pandemic with more than half (n=10, 52.6%) of respondents allocating a score of 4 or higher.

Using the ranked response data only, the top three and bottom three factors that may present a challenge to study set up during a pandemic/ epidemic are presented in figures 7 and 8 respectively.

Figure 7: Top three factors presenting a challenge to study set up during a pandemic or epidemic (n=18)

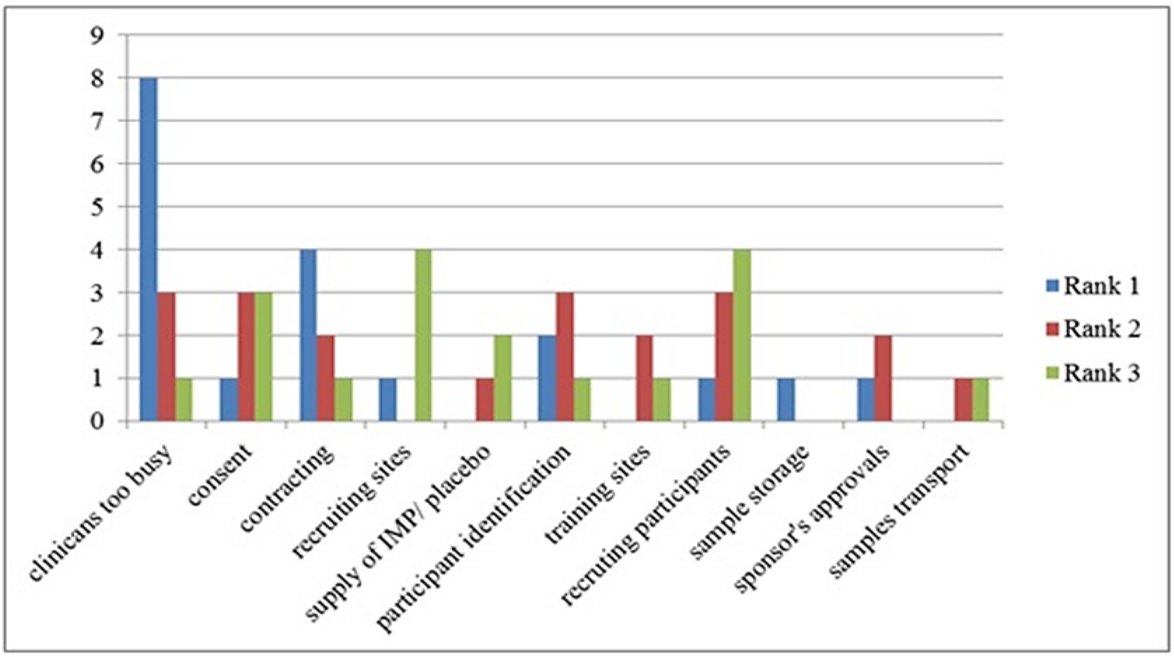
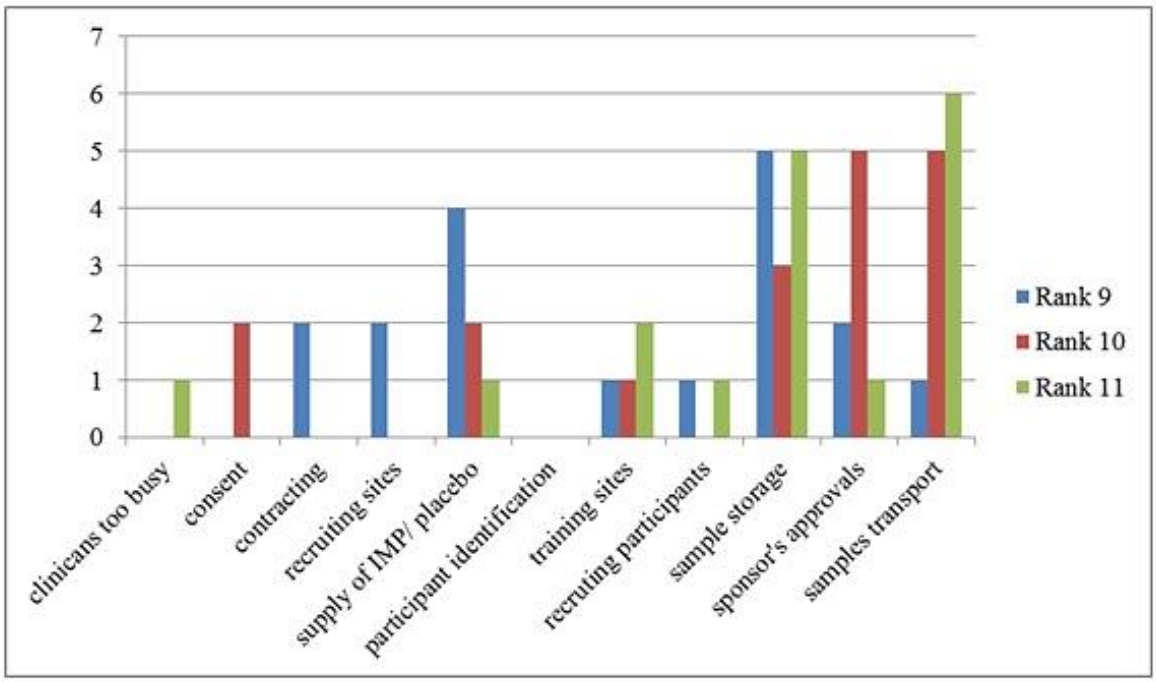


Figure 8: Lowest ranked factors presenting a challenge to study set up during a pandemic or epidemic (n=18)



Key points:

- From figure 7, data suggest that 'clinicians being too busy' is perceived as the greatest challenge. Also, consent issues, contracting, site and participant recruitment.
- From figure 8, data suggest that sample storage and transport, as well as delays linked with obtaining sponsor approvals, are less likely to present challenges to study set up. In some countries IMP/ placebo supply may also not present much challenge compared with other factors.
- Two areas in particular – i.e. contracting, and IMP supply – may require closer scrutiny, to better understand the challenge they may present in different countries.

Processes to expedite study set up during a pandemic or epidemic

Survey data collected highlighted the uncertainty of respondents about processes that may be available to expedite study setup. In particular we asked about fast track approval processes both for ethical approvals and for IMP requirement approvals, as well as whether pre-approval of study protocols were permitted and/ or waived consent (see table 7).

Table 7: Summary table of information about expediting study approvals using fast track processes, protocol pre-approvals and/ or waived consent*

	Ethics requirements			IMP requirements	
	Fast track	Protocol pre-approval	Waived consent	Fast track	Protocol pre-approval
Austria					
Belgium					
Bulgaria					
Cyprus					
Czech					
Denmark					
Estonia					
Finland					
France					
Germany					
Greece					
Hungary					
Ireland					
Italy					
Latvia					
Lithuania					
Luxembourg					
Malta					
Netherlands					
Poland					
Portugal					
Romania					
Slovakia					
Slovenia					
Spain					
Sweden					
United Kingdom					

* Red = not allowed; orange = information not available, green = process allowed

Other suggestions for expediting the setup of a study included the following:

- Preparing the public early through information provision and the media (Albania, Luxembourg, Norway);
- Training and early information for professionals, particularly for GPs, so that they would be prepared to start recruiting rapidly (Albania, Ireland, Luxembourg, Norway);
- Proactive planning about key logistics such as contracting (Ireland);
- High quality morbidity coding linking electronic records, linking consented patients to data collection and follow up protocols or documentation (Ireland);
- Early availability of protocols and study materials (Switzerland);
- Pre-assessment of potential sites in registry (infrastructure update once a year) (Austria);
- Engagement with competent authority (Spain);
- Political backing (Latvia).

Public reaction

Of the total responses (n=56), 26 (46.4%) said public reaction was likely to impact study setup, while 7 (12.5%) respondents (from Denmark, Finland, Italy, Hungary, Portugal and Slovenia) said it was unlikely to be an important consideration. The remainder (n=23, 41.1%) said they didn't know, or left the question blank.

Of the respondents who considered public reaction to be an important consideration when progressing with a trial, the following influences were identified:

- Misunderstanding of research, linked with poor communication and lack of robust information (Albania, Rep of Moldovia)
- The role of the media, in particular, in how information is presented (Croatia, Hungary, Poland)
- Reaction of politicians and health authorities influence public reaction (Italy)
- The impact on recruitment (Czeck Republic, Spain) – public may perceive benefits such as better access to treatment, or contributing to the public good, but may also perceive drawbacks e.g. perceived delayed access to antiviral or other medication, scepticism about commercial interests of pharmaceutical companies (Ireland, Luxembourg, Norway, Slovenia, UK)

Factors identified that might encourage public involvement included:

- Good scientific reporting – clarification of genuine equipoise, good self-care advice etc (Slovenia, UK, Germany)
- Clear explanation of limited effects of anti-viral medication (Norway)
- Research promotion, and efforts to raise awareness, including public information campaigns, with information presented clearly in layman's terms (Ireland, Luxembourg, Netherlands, Republic of Moldovia, Spain, Greece)
- Engagement with the media – information for the media etc. Professionals in the media (Italy, Poland, Spain)
- Financial support (Albania)

Social and cultural issues and informed consent.

Of the total responses (n=56), 10 identified being aware of social factors such as religion, ethnic, economic or other cultural issues that may impact public willingness to participate in research during pandemic or epidemic (18%). The remainder of respondents either indicated they were not aware of any of these issues (n=29, 51.8%) or left the question blank (n=17, 30.3%).

Of the participants that answered this question (n=10), the following issues were identified:

- Fear of experiments, particularly with children (Poland, Latvia)
- Mistrust of the government and in pharmaceutical companies, in particular, in conflict of interests with vaccination (Estonia, Hungary, Italy, Switzerland)
- Cultural or religious issues may influence willingness to take part and/ or to provide blood samples (Spain, Turkey, Germany)
- Economic issues may influence participation (Lithuania, Germany)

Discussion of survey

This was a small survey that aimed mainly to corroborate and substantiate available country specific information to expedite study set up.

Headline findings from survey

- Most participants were able to offer an opinion on the time frames for obtaining ethical and regulatory approvals in their country. However,

there was more uncertainty with respect to the time frame for gaining approvals from medicines regulators. There was good agreement between participant perceptions of timeframes and published (online) timeframes for some countries, but for others participant responses suggested that published timeframes may underestimate the time actually required.

- In five EU countries (France, Greece, Latvia, Netherlands, Portugal) obtaining ethical approvals for observational research is quicker and simpler that obtaining approvals for clinical trials.

- Challenges to study set up during a pandemic:
    - Clinicians' workload is perceived as the greatest challenge. Also, consent issues, contracting, site and participant recruitment.
    - Sample storage and transport, as well as delays linked with obtaining sponsor approvals, are less likely to present challenges to study set up. In some countries IMP / placebo supply may also present a challenge.
    - Two areas in particular – i.e. contracting, and IMP supply – may require closer scrutiny to better understand the challenge they may present in different countries.

- Lack of readily available information about fast track and pre-approval processes would delay study set up. Recommendation that this information is compiled and made available.

- Public reaction is likely to have an influence on the ease of conducting research during a pandemic or epidemic. Provision of clear information, research promotion and engagement with the media may be important strategies to enable public participation.

The influence of social and cultural factors on public participation needs to be better understood. Fear and mistrust of research processes, in particular with vulnerable groups, and in ethnic minority groups may present barriers to participation.

Strengths and limitations

Results from this survey must be considered in the context of the limited number of representatives from each participating country. In many instances we had a single response per country. These findings may be best understood as providing some steer for additional questions that may be useful for later stages of PREPARE research, rather than offering a comprehensive overview of approvals processes.

This was a relatively small survey that was information rich. There were some limitations to this work introduced through the design of the survey. For example, much of the factual information was collected in the early stages of survey completion and it is possible the respondents became more fatigued at later stages when asked questions that required their opinion. Pragmatically, respondents were unable to log out and then log in again to the survey; therefore a number of responses were received semi-complete. Nevertheless data gathered in this survey was useful particularly to map areas of uncertainty about procedures that might expedite the setup of a study and to clarify some information that was difficult to obtain through web searching alone. Comparing respondents' experience of approvals processes with information published by regulatory bodies, gave some insight into countries where these processes work well and less well. However there are many different reasons for the discrepancies identified, such as different time frame guidelines for different kinds of trials and/ or stop the clock procedures. Also, the information available for comparison came often from one individual's subjective experience. There was also heterogeneity across respondents in terms of their research experience and expertise. Therefore robust interpretations about approvals processes may not easily be made from these data.

Of the total number of survey respondents (n=56), a third (n=19, 33.9%) did not answer the question asking participants to rank factors that might present a challenge to study setup during a pandemic or epidemic (question 33). Of the respondents who did answer this question (n=37, 66.1%), more than half answered it incorrectly (n=19, 51.4%). When looking at the raw data a proportion of the responses appeared to have some errors. Five cases in particular were identified (from Estonia, Netherlands, Slovenia, Spain and the Republic of

Moldova). For example two respondents from the Netherlands scored some factors at opposite ends of the scale. This may either represent divergent views on this topic or an error in interpreting the question. It was also possible that some respondents had inverted the response scale using 11 as the highest end and 1 as the lowest. There was no way to confirm this however and all responses have therefore been included. Results should be interpreted with caution therefore. These findings may be better used to identify areas where more information may be useful, e.g. to understand the variability in responses about contracting, and about supply of IMP and placebos. There is a fairly consistent finding that the workload of clinical staff may present the greatest challenge to study set up.

A relatively small number of respondents were involved in this survey and a high proportion of these misinterpreted the ranking question (question 33). In the development of the survey we did not have time to pilot the software adequately, which would have avoided this problem. In future surveys when asking participants to rank questions, software limits should be set such that participants are not able to allocate the same number more than once. This would then produce better quality data for analysis. Also for future surveys, questions such as this that required participant reflection and possible deliberation might be better placed earlier, where respondent fatigue may be less likely to result in misinterpretations. It may also help to design the survey in such a way that responders can re-enter the survey to complete it rather than having to complete the whole survey this in one go. Finally, potential participants reported difficulties with the survey link. The long URL that did not link participants directly to the survey via their emails may have caused this. Consequently we may have received fewer responses than if this link had worked well.

QUALITATIVE INTERVIEWS

Aims

Using qualitative interviews, we aimed:

- To allow an in-depth exploration of areas identified of importance by researchers relevant to EARL and PREPARE
- To build on respondents data in an iterative manner as the number of interviews increased
- To increase our understanding of the challenges faced by researchers and to identify areas of best practice

Methodology

Ethical approval was sought at the outset via UCD's Ethics Committee and was granted exemption.

Design

After an initial period of consultation with stakeholders and a review of secondary literature, taking into consideration the themes already included in the survey and data from the country reports the qualitative section developed a series of relevant themes that could be discussed in depth via a series of semi-structures interviews. These data were de identified and the interviews anonymised to afford protection for the interviewees and thereby enable a more frank discussion.

Aide memoires were designed for face-to-face interviews and amended for telephone interviews. The initial interviews were conducted face-to-face with key informants. These were identified for their expertise and close affiliation with medical and health research networks across Europe. There was also an opportunistic element to this as the interviews were planned and later conducted at 'the kick-off' conference in Antwerp where many experts were in attendance.

A list of potential interviewees was constructed to represent a range of positions and experiences from a range variety of member states. Most, but not all, agreed to be interviewed. Seven face-to-face interviews were initially

conducted (FACEINT) followed by six telephone interviews with other experts in Europe (TELINT). Verbal consent was obtained for both face-to-face interviews and telephone interviews and was digitally recorded. For the purposes of analytical rigour and to recognize the continuity of responses, each interview was given a number at the time of interview and included in our transcripts and analysis. However, after a full team discussion, these have been removed in this report to better protect the anonymity of the participants. Participant information sheets and informed consent sheets are available in appendix part B.

All data were digitally recorded, password protected and transferred to a secure drive set up at UCD. Data were then transcribed for analysis.

Semi-structured interviews rationale

Interviews were designed to be loosely structured to enable interviewees to respond in their own time, at their own pace, prioritising matters that they deemed important (Flick 2006, Kvale 2008), thereby minimising (structured) *a priori* influence. The process was iterative as the interviewers followed themes that emerged in the process. The aide memoire for the telephone interviews was reviewed and adjusted to accommodate this ethnographic style of interview. This fostered more nuanced discussion around key themes.

Analysis

The data were thematically analysed longhand and further analysed using Nvivo 10 to establish themes, configurations or outliers that might emerge. The data were then read independently thus helping to further validate the findings.

The qualitative data were then triangulated with the survey, country and secondary data.

Finally, the findings were presented to numerous stakeholders for comment and verified (bar one or two minor errors) as being representative of their experiences and recognized as accurate.

Qualitative interview findings

This section provides a first stage analysis of both the face-to-face and telephone

interview data. It points up highline issues for discussion. Key themes emerging are outlined here.

Socio-Political Context

*'You almost have to know where you have come from before you can get there' (*TELINT).

The historical, social, political and economic legacy in Europe provides an important backdrop in determining the highly differentiated and complex nature of modern health care and health care systems within the European community[1]. These multi-dimensional distinctions and consequent problems are borne out by respondents in the problems they identify below. Since the phrase 'Global Village' was first coined, (circa 1964), we have come to view the idea of globalization increasingly as economic integration. Human migration and connectedness have increased at an unprecedented rate with concomitant changes in infrastructure, transportation and communication (Held, in Huynen, Martens and Hilderink, 2005). Modern transportation systems mean that infections can potentially move around the world within a few hours, as illustrated by the SARS outbreak in 2002–3 (Lee (2004).

The interview data reflected the above complexity of today's Europe reporting considerable fragmentation at multiple levels of research experiences and in policies and strategies**.** These operate at *country, regional, sub-regional* and *institutional* levels, often simultaneously, to compound the hurdles that researchers routinely struggle to overcome.

Country Differences

Some countries have a long tradition of epidemiological enquiry, others do not, and some have a less developed infrastructure and/or State commitment in terms of public health research and collecting data at population level. The interview data acknowledged and reflected many important structural differences *between* countries. These include for example, variations in regulation, health systems and health care, the composition and numbers of research ethics committees (REC's), sample storage, sample transportation, data protection, professional cultures and working practices.

While some countries like France and the UK are perceived to be more uniform in their administrative structures and procedures, others are not. There also appear to be variations and to some extent conflict between professional cultures and across working practices regarding research and approaches to research.

These variations sometimes appear to collide at the interface between the researcher, organisations, agencies and key stakeholders.

> *'I mean setting up those protocols in the UK; it's completely different from The Netherlands for instance…. If you have a flu outbreak in the UK the doctors will tell you to stay home and don't come to the clinic whereas in The Netherlands…. If you go to the new European countries the doctors will definitely see those patients, well there's two sides to that of course. So the policies are different in different countries' (*FACEINT).

It was apparent that this also translated into different health care treatments being offered in different countries.

> *'But also…. if you look in Europe what happened during the last pandemic, 27 countries, and look at the 27 health councils or their equivalent in all these countries they all gave different vaccinations. In The Netherlands it was 2 vaccinations, so closing the schools yes or no? So all these kinds of things…. And all based on the expertise of a small group of people on the health council…. and it's funny to see how in a country like Belgium, which is just next door, Antwerp and Rotterdam are working; I work in Rotterdam, I live in Antwerp and this was two different worlds. So that here they vaccinate only once and many things were different and then the press starts to ask, or the public at large wants to know what's the right thing to do'* (FACEINT)

Substantial differences in regulations between countries were also recognised.

> *'Because different countries have very, very different regulations and data protection things like sample storage or storing data for further analysis at some other point are very, very difficult in some of the countries that our centers are located in'* (TELINT).

> *'So this is the scenario then; you have all the peculiarities of each country; there are countries are better organised and other countries are less well*

organised but to get all the general approvals for any study takes you many months if not more than one year' (FACEINT).

These discrepancies present a series of challenges for all researchers. However, this may weigh more heavily on junior researchers who often have to undertake the preliminary access to research organisations. The data here suggest that clearer guidelines would better facilitate the process,

'I am actually a relatively junior researcher which means in fact I am often the person who has to communicate with various institutions. It's quite often not the most senior people on a project that does that…. My personal belief is that in itself it can be a little bit problematic because even though I have very rapidly gathered experience of how to do things, in actual fact the sole fact that its often junior research staff who are quite heavily involved in putting together documentation and so on, means that often the awareness of the people putting together documentation of potential issues is perhaps less than if they were in situations where there is more senior input. So that perhaps is the first starting point' (TELINT).

Less experienced researchers who feel disadvantaged by not having more senior input to steer them in the early stages may benefit from being offered more guidance in the early stages. Differences across countries appear to penetrate most aspects of the research process, for example, regarding data protection.

'One of the one's that is particularly difficult in is (Country X…). For some reason they're having lots and lots of difficulties to convince their authorities that it is a worthwhile undertaking and that it is something that can be done in such a way that it wouldn't be problematic' (TELINT).

A number of difficulties were reported around taking and storing samples. For multi-site research (particularly if it has an international dimension), having the appropriate equipment and instruction were perceived as important issues. In some countries, facilities were reported to be under-funded and under-resourced. The data also pointed to a general lack of information in relation to what countries have what type of facilities and if they are fit for purpose. This may create a major obstacle.

*'So despite the fact that we did write in the protocol the freezer requirements, we were inundated with the same question about, 'we have not got a minus 80 freezer; we have only got minus 20 is that enough? This was deemed to contribute to serious delays,… Well it's actually in the protocol but we sent out a ten-page protocol that they had officially been asked to review within twenty-four hours. So to be fair to them they were going to miss things and actually the people who were delaying things the most were the laboratories' (*FACEINT).

Regional differences

Regional differences were said to exist which added to the barriers and sometimes to public confusion. For example, in the case of advice on vaccines;

'And then if you look at the difference even in Belgium you have the Flemish and you have the French-speaking people, if you look at vaccination coverage and the advice, etcetera. So basically the French speaking people they look at the French television and listen to the French radio. Now where's the Flemish? The same with the Dutch so if you look at, so we had the vaccination coverage among the people at about 70% and the same was true in Flanders…. So the coverage was about 15% just from the top of my head and that was similar to France. And this is within one country so you see there are these regional differences and what we should have good European recommendations if possible' (FACEINT).

Additionally, ethical approval applications demanded more time and resources depending upon which country approval was sought when sometimes it was possible to go through a centralised national system (passport) applicable to each region and sometimes not.

'So now actually you send everything to an ethics committee that works at the county level; so Switzerland has lots of different little counties – there are 26 of them and not every county has their own Ethics Committee but there are basically a few Ethics Committees and its sort of you can find out for each county that you work in which Ethics Committee you are supposed to send stuff to' (TELINT).

Sub-Regional and Institutional

Even within regions our data suggested variations between institutions. For

example, hospital trusts in the UK often have different policies and / or interpret the same information differently. This complicates and slows down the research process.

> *'We still have to have individual research R &D approval in each individual Trust and that can be very slow'* (FACEINT).

> *So, for example, in this project there are 20 different sites from 16 countries and some countries have a National Ethical Approval process but most in Europe don't. So you would have to go through Ethical Approval for each of the individual hospitals, and then that hospital will have to obtain Ethical Approval from their hospital or their Regional Centre.* (FACEINT).

A very common finding relates to a profusion of agencies combined with a lack of clarity on *who to involve* in research, *why*, and *at what stage*. Experiences in the UK and Switzerland are very different, for example.

> *'So I think first of all there is often a kind of profusion of different institutions and different aspects that you have to really take into account. Lining up everyone that needs to be informed of what it is that you want to do that is quite difficult in the first place is often unclear and probably more true in (Country X…) for me personally than in (country Y…). But it is often completely unclear to me why I need to involve people, who I need to involve and which stage I need to involve them at'* (TELINT).

A further point relates to the difficulties researchers may have in how to categorise their particular research project in advance. This knowledge is a necessary first step in order to establish whether an application for ethical approval is necessary or appropriate. Determining at what level and which agency to approach is important. While there may be clearer guidelines in some countries these appear more ill- defined in others. This is perceived as a basic problem in terms of some projects discussed. This has time and resource implications in terms of the necessity for ethical approval application or not. Research usually requires ethical provision, yet surveillance usually does not, for example. Before researchers start applying for ethical approval they need to know the most appropriate route and which agency / network to approach. The classification of the project is crucial at this stage, i.e. service improvement, surveillance or research, and has time resource implications.

'From the time you are ready to submit and you have all the documents, when you have finished the Protocol, the SOP's, the CRF's and you say; Ok, I'm done, let us start all the processes. It will take you through such a huge network and to get all the centres' approvals it may take you one year or something like that' (FACEINT).

The data suggest that there is a risk of unnecessary duplication, for example, different bodies continually 'reinventing the wheel' across Europe. Again, this reflects a need for clarity regarding basic information on application processes from RECs, research agencies and other relevant bodies.

'For some, even before a researcher approaches a particular committee, it may be indeterminate which is the most appropriate committee to approach. For example, how research is categorised…., as 'research', 'surveillance' 'and service improvement'? Thus different ethics boards may have different definitions of research. A project may be categorized as research in one country and surveillance in another. Again, this points to the needs for harmonization. In fact, we couldn't actually get them to a research ethics committee in the UK because they, to some extent, quite rightly were saying that it wasn't research; it was surveillance and because it was a project that was dealing with improving surveillance methodology for children this can be quite problematic in terms of how to frame a project that can often cross multiple boundaries for someone who is kind of regulatory or ethics kind of individual to understand what it is that you are doing and whether or not they are the correct instance to kind of get back to' (TELINT).

'In that particular project (Y…) we then also had the difficulty, which I am sure several people have mentioned who have worked on European projects, that actually to some degree whatever was true and valid in the UK, didn't really apply in some of the other countries that participated' (TELINT).

This case was reported to result in the lead research country being unable to offer relevant documentation to research centres in other countries because they were exempt from ethical approval in the lead country.

'So some people were left with having to go through the ethics approval process not knowing very much about the project or not knowing as much detail

as obviously was available to us as the lead center and that created some difficulties.' (TELINT).

A further consequence of this disparity in classification across different countries resulted in certain countries having to spend research funds on ethical approval when other countries did not. This created some tension within the consortium.

'So if you look locally at all the countries you start with one protocol with one clinical protocol, with one set of SOP's etc. and at the end of the approval process you have several different versions adapted to each of the center / countries, so regions within the countries which is stupid, absolutely nonsense…. Sometimes the difference you get one Protocol, in the other of another country just the opposite of what they wanted. Some center's requested to put out things that other center's requested to put in. So there is no clear rationale behind those changes' (FACEINT).

The content of the above quote was echoed in the data as a cause of concern and frustration. Disquiet was also expressed that there was an overall reduction in clinical trials in the UK, The above documented concerns over disparate and unruly regularity issues may be an important explanatory factor here.

Ethical Approval Systems, Regulations and Configurations

*'County (X…) is quite different from the (country Y…); so (country Y…) is extremely bureaucratic; I mean my experience of (country Y…) ethics process has been that I have wanted to lie down and die several times' (*TELINT*).*

Ethical approval systems appear to be a major barrier to many researchers in most countries for a number of reasons. The above quote succinctly captures the sheer frustration of navigating them. Some have labelled the process as '*Ethicide'*.

'So trying to obtain and coordinate ethical approval for 20 different sites is complex and all of those take a long time and it can take even for very straight forward observational studies 6-9 months or even up to a year to be able to open all the different sites across that time' (FACEINT).

And,

'I have tried that locally many times; I have made tons of suggestions; I have had tons of direct confrontations with my local Ethic Committee because I am not an expert but I am experienced so I know many things' (FACEINT).

Ethical approval requirements are reported to be more stringent in some countries than in others. Furthermore, concern was expressed that the process for observational studies is out of proportion to the risks involved when compared to interventionist studies.

'What is worse, the mechanism as far as I am aware of it, is the same if you run just the pure observational study or if run the control trial so there is no difference in the complexity and on the risks from the ethics perspective of this kind of studies' (FACEINT).

The data also indicated inherent problems when using standard protocols and implementing these in different cultural contexts across Europe, especially if this was not given prior attention due.

'In terms of communication I think that's another aspect that is quite often not managed very well in these large international projects and we certainly didn't do it very well and we will probably have to go back and look at this again and do it differently. I think we left the centre that were working with us a little bit out on a limb because we didn't really gather the information like you are doing now beforehand. We just assumed that somehow this was going to sort itself out' (TELINT).

Rising costs of conducting research and fees such as REC application costs was also highlighted.

'Now it is going like the UK, becoming standardised and quite expensive' (FACEINT).

In addition to costs, the move away from local committees and the introduction of a layer of non-medical or health professional personnel who are disconnected from the epistemological context but who are part of the administrative process was also viewed as sometimes being problematic.

'Often there are very complex reasons I think and social constructs around that. I think that has still been slightly less well understand at a European level in this

type of study where you have got a very standardised protocol that is being implemented in different countries all across [Europe]; so I think adding some qualitative assessment in terms of not only of the barriers related to the administrative and the ethical and financial barriers' (FACEINT).

However, there was some evidence that the route to approval may not always be a negative experience and some good practice was seen to exist.

'So myself and another colleague went to the Ethics Committee and actually that went OK. The local REC (X….) was fantastic and very supportive. We had to make a few changes but then they appreciated that we didn't have the time to turn up again in person and they were happy to do and accept the changes that they had suggested via email and to sign it off and to give it the Ethical Approval that it required' (FACELINT).

And,

'There are other countries that once you overcome the initial steps then and once you get the approval everything are quite easy. For example, the UK; the initial application may be a bit more accomplished than other countries but once you go through to get the approval you can extrapolate that approval to any other participant centres and it is recognised within the country so all the hospitals can be joined to that particular study without specific application' (FACEINT).

And

'In the UK so it making great strides; most of what I have been talking about is more at the European level rather than at a UK level. So the regulatory approvals are still cumbersome in the UK, but are getting better. What we have now, of course, is Universal Ethics, which is great. So we have the Research Passport, which does, work and most of my researchers do use that to go to different sites when they go across to different sites' (FACEINT).

Recruitment and Informed Consent Procedures

Recruitment and informed consent procedures (RICP) proved to raise substantial and complex concerns. The data calls for a review of informed consent procedures

across member states. There appears to be a need for better-harmonised approaches to informed consent across Europe for the differing types of studies, including observational and intervention studies, and types of consent required for disparate types of patients depending upon age and competency. There are reported difficulties in relation to the limits of consent and with limits for accessing data retrospectively either though death or an unanticipated clinical research need.

One interviewee gave an example that may offer a partial solution for routine procedures at least;

> *'So in Switzerland at a hospital you can apply for basically global consent [in this case with children]. So in my hospital in (X…) when you come to the A&E or you are admitted as a patient, then you will be given a consent form. Every parent of every child who comes through the door will be given a consent form to say, would they be happy in general for anonymised data to be used in research. They can then say they wouldn't be happy and that's fine and the patient's notes will then be marked and that generally is also very much respected that you then don't include these patients in any projects…. If they say they are happy then the sort of demographic data and clinical data, just anything that can be found in the routine documentation, including routine tests can be used for research'* (TELINT).

The 'light touch' with regard to RICP for some types of research was largely welcomed.

> *'Some countries already have an established system that requests general consent on admission to A & E and hospitals for routing samples [in paediatrics]. Although this does not include anything in addition to routine care it may point to a useful principle'* (TELINT).

> *'I have not yet had the experience on a European wide level but I see the regulations are getting very frustrating and obstructive for just observational studies, for example, with material that is available. Even then I think they are requiring informed consent of patients for use in retrospect data that is stored anyway. So that is in my opinion a very unwanted situation…. because none of these patients is really afraid of what we are doing with their information; its*

just that the other sites feel that there is a law that should be adhered to. I fully agree with the regulations around intervention and experimental antibiotics but I have problems with cluster-randomised approaches and problems with the strong rules for observational studies' (FACEINT).

There are also other fundamental cultural and organisational concerns. The data pointed up an important link between research protocols and the organisation of health care systems. It was considered problematic to apply rigid protocols (one size fits all) in a universal manner without being cognisant of the specific health care system context. For example, in a country where there is no / or limited free access at the point of need:

*"There's an organisation that wants to come and use our country as a recruiting tool. They want us to change our flexible protocol to match their inflexible protocol, which we are not particularly keen to do, but that organisation doesn't seem to realise that this will affect recruitment…. The lack of understanding into that is quite astonishing. But the background from that study group is working on another infectious disease, which is chronic so the patients have nice routine regular opportunities for sampling and the patients, if you like, are indebted to regular medical treatment in keeping them alive… So they are approaching the problem from a very different tradition because those of us that work in outbreak such as influenza and bronchiolitis of infancy; well we have learned that to get consent and to get your samples you have to be incredibly flexible and take what you can when you can get it' (*TELINT*).*

Transactional Consent

The above vignette also illustrates the potential of transactional consent when consent is traded for treatment and care. However, in an epidemic / pandemic situation other factors need to be considered. Taking consent in this scenario is different to taking routine consent.

'In relation to epidemic / pandemic research those normally health individuals who don't have a background in being medicalised' just to be sick and in hospital is a shock to them. The fact that they are sick and in hospital with a new unknown disease which is a pandemic disease is pretty terrifying.

So to try and get consent from these people you have to an approach them with a great deal of care and sympathy' (TELINT).

It was stated that because of the sudden and severe nature of the serious infectious diseases families often wanted significant amounts of information that more junior clinicians may not have or they don't have time to answer. One clinician recounted that to gain consent they felt they had to spend considerable time with the family explaining the illness and procedures (usually 20 – 30 minutes) after which families were usually keen to support their research. Thus, informed consent is related to trust and information and is relational. This was reported to rest on senior physicians being willing and able to take time. One interviewee stated that in a past example of H1N1 only senior people (above junior doctors and nurses) were involved in obtaining informed consent. Hence there appears to be a transactional nature to the process. The transaction here being information exchange, based upon trust, transparency and patient co-o peration.

Another point arising from the data was the inclusion / exclusion criteria for research. In one country at least, an important criteria for clinical trials research appeared to be citizenship status. In a globalised age with considerable migration patterns within and between member states there is obvious concern that sections of the population may effectively be disenfranchised.

In addition, consent in some countries was held to be related to the ability of the public to accessing medical services where they might not otherwise easily obtain them.

Epidemic / Pandemics and Rapid Response

The need for a rapid response in the case of epidemic or pandemic has been well made by PREPARE and others. However, there is little evidence available about the experience of most European countries as indicated in the country and survey data sections of this report.

Under extreme public health emergency circumstances there are important precedents to expedite clinical research. The qualitative data suggested that these precedents may be of value in terms of adaptation for future PREPARE policy/practice recommendations in this area. For example, in the case of

Switzerland, when it reported that consent for research associated with routine procedures is sought from all parents of children on admission to hospital.

> *'The possibility for pre-approved consent with clearer parameters appears to be more straightforward for some diseases, for example with measles which has a high degree of predictability,… now in the bible belt, we had an outbreak of measles, we have about 3,000 reported cases. We have predicted more or less, say 3, 4 years ago, we already had our protocols ready in, similar to what we are doing here. Therefore if we have an outbreak in that community what can we do? So we cannot vaccinate, we cannot treat them properly'* (FACEINT).

The above quote relates to being able to prepare for well-known infectious diseases but also points to how particular cultural and religious considerations can affect uptake regardless of pre-approval. However, having pre-approval it did allow research to occur.

Some countries reported that they have been able to expedite normal routine procedures in response to an outbreak, but only when it was classed as a public health emergency. The UK in particular appeared to have gained valuable lessons as an instructive case study relevant to PREPARE when various factors coalesced to accelerate the research process.

The data suggested that serendipity played a part in the UK experience and ability to respond rapidly to an outbreak. In the first instance an early network had been established on the basis that a flu epidemic was recognized to be a high public health risk just prior to an actual outbreak.

> *'After a series of public health emergencies including, fires, floods, Foot and Mouth and fuel disputes in the UK, it developed a Risk Register when Influenza was at the top of the list'* (TELINT).

Public health regulators may have room for maneuver, i.e. during a public health emergency. The UK Public Health Agency allowed research to be conducted via classing it as surveillance during a public health emergency. A small but experienced and committed group of medical personnel (specialist physicians) met who were to act as advisors to the Cabinet and who formed a 'spoke and hub' network across the UK to include a range of hospital sites and staff (research

nurses and doctors). This allowed the same research in different regions with a dynamic feedback loop between clinicians, areas and government. Once the flu outbreak occurred they were able to effectively maximize the prevailing network as the physicians agreed to work collaboratively to reclassify and perform a *real time analysis* of clinical characterization work and tracking the disease. The collaborative nature of the researchers was viewed as crucially important here.

This flexible and pragmatic approach by the key actors to existing regulations further encouraged a quick response.

> *'We found first of all the other unusual feature of this network was that the primary purpose was not to conduct research as a means to an end. The primary purpose was to inform policy making; so our data was reported back to a cabinet office subcommittee on an alternate weekly basis throughout the pandemic'* (TELINT).

> *'However, so I slightly short-circuited the system and I will be quite open on this'... Me being me and not knowing all the details about the expedited system in advance and having not met our Research Services person at that moment in time, I did what I thought was right and went for the national level to make sure we had their support'* (FACEINT).

Personnel at high levels of government agencies interceded to influence the cooperation of hospital Trust managers *via* excellent networking, which utilized individual communication between known actors. This was described by one interviewee as 'the human factor' and was seen as being of primary importance. The specialist physicians also contacted the Trusts by phone to ensure co-operation when necessary. Thus, top down Government pressure was exerted on Health Trusts by Government agency staff that had 'clout' in terms of funding the institutions.

Initially the enrolment of patients was not an issue as the research was deemed as a public health need and as surveillance not requiring ethical approval. Later, for another related study requiring intervention consent was necessarily sought and was described as 'transactional consent' described as a process with a trade-off between experienced research staff (senior doctors and research nurses) offering time and information and dialogue with patients and

parents/family frequently resulting in consent been offered.

Thus, this public health approach allowed latitude for observational research in times of crises.

Networks

Networks were identified as being of major importance, central to both local and international research and operated on the basis of a combination of factors such as shared knowledge/training, experience; area of clinical expertise and area of methodological expertise. Tacit knowledge, trust, mutual interest and commitment of researchers were seen to carry significant influence. In short, a communal medico-clinical research culture. Research clusters therefore have developed on the basis of linking in with commonly *experienced* and *trusted* research colleagues.

*'Knowing the right kind of people is often helpful' (*TELINT*),*

'The reality was that all the people in the room new each other and had a relative degree of trust…. There are a lot of people out there that have a very fluffy approach to this that think because it's funded it's all going to work well. Human nature and approach to collaborating is much more down to personality and trust….' So I think, well I put an emphasis on the fact that we as a group respect each other and trusted each other.' (TELINT).

I only know if I have problems with any issues regarding a study, I ring our leader' (TELINT).

When it came to international collaboration this principle was also applied when setting up and conducting research. The importance of the local person 'in situ' was a key consideration and was also considered important in overcoming any language or local cultural problems that might arise.

'My experience in other countries is, it is more about the contact person there you know what I mean? I contact the ethics committee not directly so it's about a person, an investigator and they do that [a local investigator make the application process and are trusted with the process' (TELINT).

Research therefore appears to be conducted via strategic alliances, most of which

appear to develop organically among researchers often hinging on particular skills and institutions and position within the organisation.

'If they have their special lung physician it depends on relationships between the persons in the hospital. It is a very individual; we have really good contact persons so our network is really good. But if we haven't the right contact there in the hospital maybe it's getting more problematic or so but that we will see. This has to be taken into account' (TELINT).

The recognized general role of networks in research appeared to be of special significance in times of epidemics or pandemics.

One of the perceived benefits of the network was that key personnel were able to expedite research by circumventing the normal ethical process and standard operating procedures (SOPs). While this is clearly not standard protocol there are conceivable emergency situations where extreme measures need to be taken. In this sense there might be an argument for setting up emergency procedures over and above SOPs.

'We then managed to…. short-circuit the system,... We looked on the website so where the next REC was meeting in (X….) So we contacted the chair directly and said will you see us this week because we are in a rush, and he agreed, and he did' (FACEINT).

'I do think that human factor does help when you are trying to work something out in a hurry and you don't want people to turn round and say; well no we're not happy to integrate this or work with you over it' (FACEINT).

*'I think it is therefore sensible… to look at the key decision makers and how those decisions can be made about trying to sort out the of speed approvals so that within a few months happening then trials could be set up but, also going through the regulatory and ethical processes. They would be different in different countries of course, but I think the UK is a reasonable place to start to do that' (*FACEINT).

However, a perceived problem with being part of a collaborative network relates to current contexts of research when the Government and Academic climate is based upon highly competitive models to research funding allocation. This shapes

how researchers and clinicians are rewarded in terms of promotion and prestige and does not foster sharing of knowledge, experience or intellectual property.

> *'Until the government that allocates research money, moves away from this model of highly competitive grant awarding. It's not just the reward it's the way they competitively recognise being the first author or last author as opposed to being a collaborator. I don't see how that is going to get better, especially in the UK and America there is no points for being a collaborator; there are only points with being a Chief Investigator*' (TELINT**).**

This may present a real blockage to collaboration within and between countries. The data also pointed to the possible need of widening these 'organic' established networks of researchers, 'knowing someone' so they can become more inclusive, incorporating 'people who understand the problem' (TELINT). For example, identifying researchers who may not be networked at the highest levels, but who can build capacity around their particular expertise.

> *'So I think my wish would be really for more people who understand the problem and not quite so worried about people who kind of know me or know other people that I work with…. I think they are also very valuable because like you are probably finding now there are often lots of people in a network and many of them will perhaps have had a similar experience to a specific problem that you are encountering and you can actually build on that; whereas if everything is fractured and individual then everyone has to start from scratch with every problem*' (TELINT).

> *Thus, there is a suggested move, from personality-based networks to knowledge based networks. 'Knowing someone versus knowing someone who understands the problem'* TELINT*).*

Communication

Communication as a broad and crucially relevant topic featured throughout the data, falling here under headings of language, public engagement, communication between researchers and information needs.

Language

While language has generally been regarded as an important barrier to collaborative international research this may not be regarded as the obstacle it once was. New computer technology that can provide suitable translations and the prevalence of English as a common working language has helped to some extent.

*'The best language of course is English' (*TELINT*).*

However, some concerns pointed to issues relating to on-the-ground (local practice, local review and local acceptability) interpretation, dissemination of information among wider staff members as well as the costs and time involved.

Our experience of that is that can be expensive because that is a cost because that then has to be translated, of course; so all of the protocols have to be translated. Then it has to be adapted for local practice if you like, local acceptability and then has to go off to the Regional which also charge as well and it takes time as you would imagine' (FACEINT).

The data indicated several existing forms of single and multi-site collaboration, including for example, collaboration within roughly the same language group, but also wider collaboration including different language groups. Collaboration between established member states was regarded as being less problematic than collaboration with newer member states and other countries outside of Europe in relation to language matters.

Public engagement

The idea of the need for public engagement is not new and has undergone several incarnations. During the last half of the 20th Century the importance of the relationship between the public and science and medicine formed an increasing plank of institutional policy by major research funding bodies and governments across parts of Europe following the Bodmer Report (1985) (See Ziman 1991). To a large degree, this was a pragmatic policy reaction to an identified lack of trust and negative attitude to science and medicine, for example, The Eurobarmeter, regarding biotechnology and the EU's formation of groups to address 'the problem' in the 1990's, when public 'buy in' was viewed as politically expedient in a global competitive environment.

It arguably 'began' with a 'deficit model' approach where the public were held to be deficient in scientific knowledge and given scientific information and expected to learn it in order to become scientifically literate and accepting of science and then evolved to more sophisticated institutional models of the public which moved from perceiving 'literacy' to be the goal to 'understanding' by the public and then to 'engagement' with science and medicine.

In essence, the public were gradually recognised to have credible sets of knowledge's that were useful in collaboration with 'expert' knowledge's. Trust and institutional transparency were (and continue to be) seen to be of more import to a socially situated risk situation than detailed scientific knowledge in areas such as, radon, biotechnology, GMO food, the use of blood products, vaccination policy and various other areas of risk.

This move was influenced by authors writing in the area of the Social Theories of Risk literatures and the Social Studies of Science and Technology and not least following a series of industrial disasters such as Bhopal, Three mile island and Chernobyl, as other, more recent social risks to public health came to the fore, public reaction became increasingly important to governments and government agencies. See also, Kasperson, *et al* (1988), Zinn (2004) Wynne (1992), Krimsky and Golding (1992)

These factors are directly relevant to the aims of EARL and PREPARE in the context of the relationship between the public, patients and the stakeholders with a concern to engender public trust and co-operation before and during any epi/pandemic situation in Europe. The broader context has resulted in the recognition of many positive outcomes of an early involvement with the public and patients preferably at the beginning of projects, even at the proposal phase.

Failure to adequately involve the public may have negative consequences as was the case in Feb 2014 when the BMA urged the UK government to increase public awareness of the implications of patient data sharing, following concerns among GP's that almost half of patients were unaware of the plans by the NHS England to share some data from GP medical records. As a result, and after a huge amount of financial resources and time had been spent the plan was put on hold at the eleventh hour essentially because the role of the public had been neglected or at least been taken for granted (BMA Feb 2014). http://bma.org.uk/news-

views-analysis/news/call-to-boost-public-awareness-of-data-sharing). This was also interpreted by various groups as a breach of trust and loss of face. The moral of the example being that it is important to take the public as a serious actor in the network when planning research project's including PREPARE.

Two further cautionary points relate to the problem of defining 'the public' perhaps best approached by viewing people belonging to different, non-homogenous groups who operate as flows rather than as fixed categories and treated as a 'thing' (Wynne 1992).

The second relates to how news events for example, the news from Ireland regarding the historical unethical use of children as research participants without consent in vaccination trails in County Galway. (http://www.independent.co.uk/news/world/europe/ireland-mass-graves- archbishop-of-dublin-calls-for-full-inquiry-as-evidence-of-medical-experiments-emerges-9513101.html, June 2014). Also, wrong information may negatively influence public trust (Barrett, Moore and Staines, 2007).

So timing of PREPARE initiatives needs to be alert to wider public contexts operating outside of research agendas.

The data similarly promotes the view that a two-way process involving the public in negotiating the planning of research is a vital component. It is more likely to provide realistic models of how the public is likely to react and/or co-operate or not. It is also more likely to result in the increase of trust that may also optimize public buy in.

One respondent highlighted a recent experience of involving members of the public at an early stage of research in focus groups. It was the first time s/he had experience of this and discussed the very positive outcome in terms of the research benefits of understanding user acceptability of the planned research.

In addition, the data has suggested that a mature dialogue with patients and parents of children has positive research benefits if it is done with adequate time resources by experienced staff. For example, in what was earlier referred to as 'transactional consent' in the Report section on consent and here.

'My experience has been that parents are remarkably willing to engage with that process because in general parents feel very strongly about wanting the best for their child. If you can engage them and explain to them that what you're doing is exactly also seeking the best for children like theirs, then my experience has been that actually they are very approachable and they will often say yes' (TELINT).

However, the survey data suggests that researchers often work under pressure and lack of time presents a challenge to best practice.

'It has worked very well for us; there are a number of things that we have learnt from that which could have made life better for us. We could have done the priming; the hospitals in the first place they didn't understand what X Network was; they didn't understand some of them what we were really trying to do. We put together FAQs which has since helped with that and that was circulated nationally but it would have been good to have done that in advance of pressing the button but you live and learn and we were in a rush in the end' (FACEINT).

Communication between researchers

It appeared that in the challenge to organise a research project the issue of communication between researchers was also something of a Cinderella in the priority list, something taken for granted and left behind. It seemed that it was assumed to be unproblematic but in fact became the cause of problems and delays as information vacuums developed.

In terms of communication I think that's another aspect that is quite often not managed very well in these large international projects and we certainly didn't do it very well and we will probably have to go back and look at this again and do it differently.

'I think we left the centre that was working with us a little bit out on a limb because we didn't really gather the information like you are doing now beforehand. We just assumed that somehow this was going to sort itself out' (TELINT).

As the above quote recognizes, the lead researcher may need to ensure that some

centres are not left out in a limb because of inadequate communication practices well thought out beforehand.

Information Needs

The need for reliable and timely information/communication appears to span across the different groups, that is, between researchers; medical/researchers to publics and patients and from government agencies to both researchers and various publics and other stakeholders. During times of epidemics or pandemics this need appears even more crucial. This needs to be discussed and planned well in advance, via a tried and trusted dissemination structure. Again, the UK example above relating to GP patient data sharing shows how the plan for dissemination failed spectacularly resulting in the project being put on hold.

In addition, one respondent highlighted a country case where mass media (Television / radio) reception allowed different and conflicting science policy advice via different country channels within the same area. In the case of an epidemic/pandemic the results of this would result in confusion for publics needing reliable, consistent advice. It is not clear how this might be avoided but it seems a case for further consideration by PREPARE in terms of public health agency advice co-ordination.

Intellectual Property, Collaboration and Competition

In recent years the research process has developed into a highly competitive industry and one unintended consequence of this is that the increased importance of intellectual property (IP) has made collaboration more difficult and unlikely. This is to a large extent driven by financial incentives and the introduction of and reliance on university metric systems. One respondent was concerned that researchers would be protective of their data to the determent of cooperation.

> *'…this is my data I am not going to tell anybody until it's accepted in the journal'* (FACEINT).

However, there remained a reported a high commitment to research and the value and need for collaboration.

'I look at some of my colleagues and think the incredible amount of altruism that's been shown and the people that are working on the ISARIC project the vast majority have not been paid at all or not under any academic recognitions with what we're doing and yet are still quite committed to doing it. I think that's ultimately maybe another source of frustration' (TELINT).

The advantages of collaboration are thus recognised as being crucial in public health emergencies.

A cautionary note here is the expected role by PREPARE of using some individuals and research groups as research sites for PREPARE research in terms of intellectual property, academic careers esteem, and rewards when they perhaps feel somewhat disenfranchised from membership of PREPARE. It may warrant some consideration at an early stage to ensure that assumptions of collaboration hold true and that experienced researchers do not feel overlooked or fear that their role will not be adequately valued and rewarded.

Political Economy of Research

The data contained many instances when interviewees spontaneously reflected upon the role of political economy, when unease was often expressed about the relationship between industry, politics and research.

High financial costs were reported as a key barrier inhibiting the scope and direction of research outside of what was generally termed 'Pharma'.

'I think the sampling and shipment could be improved, but that's just logistics, and that's just money: so you could get FEDEX; so that's not a problem. Much of the reason why many samples are slow and our process of shipment and organisation are purely around cash really. So certainly that has been demonstrated... that if they want to move samples that can be done' (FACEINT).

Excessive university and institutional overheads (bench costs) were also cited as a problem.

'There is also one study where the university wanted to have one hundred per cent overhead; I said oh my god. Therefore sometimes they decide to participate and industrial trials because there are a lot of fees…. I think doing research in (country X…) is not very easy, medical research, because the government does not provide a lot of external funding. This mainly comes from the European Commission or from private institutions' (TELINT).

Hence, industrial research was recognized as being better funded and efficiently financed, governed and staffed when compared with state sponsored research.

Outside of industrial research there is generally perceived to be a shortage of research staff as represented in both the quantitative and qualitative data. In addition there appears to be limited scope for continuity of staff because of the nature of employment contracts. Short-term contracts militate against continuity of research. As contracts end research staff may move elsewhere, therefore skill sets; experience and knowledge may be lost. The issue of staffing contracts may also be compounded by 'bench' costs,

'…the second point is not enough staff for doing all clinical trials and the physicians, of course, but also its ongoing the universities. They look at how much fee it is and the universities they start to include overheads too or they want to have a fee for long time activation; that's new for me' (TELINT).

There is scope for discussion on the nature of researcher employment contracts and continuity of employment.

Others pointed to cases where ostensibly the issue was about research, for example, the export or import of samples, but where broader economic or political concerns were involved albeit if institutionally unacknowledged, for example, in the production and distribution and payment of vaccines.

'this is all an industry, an industry hoax so they really want to sell us the vaccine that we don't need' (TELINT).

A further point related to the perceived need for governments to be seen to be in control sometimes creating situations during epidemics where the science was over ruled by political expediency or simply over reacting and stock piling vaccines. This was called 'PR' by one respondent.

Discussion of interviews

According to the Commission, the number of clinical Trial applications in Europe has fallen between 2007 and 2011 by 25%. At the same time, costs for bureaucracy and resource requirements to handle paperwork have doubled, and delays have increased by 90% (www.janssen-emea.com/node/474[1]).

The relative decline in clinical trials requires careful examination. Key issues raised in the qualitative data included, problems in definition, i.e. what type of research is being conducted? This determination is crucial at the initial stage since it then determines which ethics committee documentation should go to. This is a common potential blockage and has implications in terms of costs (amendments are costly) time (it holds up the process) researcher burden (resulting in wasted effort and frustration).

Harmonisation and Bureaucratisation

The EU report (Directive 2001/20/EC) of 2001 began a process of clinical trial harmonisation. The latest version of this is the Clinical Trials Directive 2014, operational from 2016. The data reflects on one level a commitment to harmonization but on another concern about the more pragmatic implications of harmonization at local level.

There is some anxiety about what is perceived to be top-heavy bureaucratisation and ceding power to authorities that are remote from the problems. This is experienced as 'frustrating' by researchers, particularly in emergency situations where a speedy process in necessary. The data pointed to the issue of swift research having depended on effective organized networks and professional collaborations. There is, arguably, then a tension emerging from the data between the benefits of harmonisation necessitating increased bureaucratization versus the loss of interaction of local knowledge and local networks. For example, one researcher said that previously an ethic's committee staff member accepted a document with the wrong version number on it because of her familiarity with the researcher and trust and simply changed it. In contrast, such human error

[1] This evidence goes some way to reflect the European Commission's attempt to reverse the recent decline of clinical trials conducted in Europe www.janssen-emea..com/node/474).

now results in the document being seen as unacceptable.

Furthermore, harmonising procedures may need to take careful account of differences in terms of socio-economic and cultural values and how health care systems are structured and organized in and outside Europe. How standardized procedures are implemented and received by the different stakeholders will vary across countries and cultures and as one respondent pointed out protocols need to be flexible to some extent – setting the parameters of these may make 'the devil is in the detail' a truism.

Also, not all research is the same. The data points up important difference in types of research normally conducted, ranging from observational studies to clinical trials with intervention. Ethical committees could be cognoscenti of these differences and they may require different treatment in terms of ethical consideration particularly in emergency situations. For example, some have called for ethics committees to apply a 'lighter touch' to applications that are observational studies.

CONCLUSIONS

Taken together a number of key issues are emerging, some of which are reflected in research carried out to date. Due to the significant variance in processes required to secure ethical approval amongst and within countries and the actual time frames involved, some level of pre-approval of research protocols is essential in order to increase the feasibility and success of the project. In addition careful consideration of issues related to public education, processes of recruitment, clarification of appropriate levels and methods of consent and allocation of funding resources will be required in advance. Significant focus must be given to the classification of the research from the outset as this will exponentially affect the logistical and process issues involved at many levels of the study. This issue will be further intensified in light of the two legislative changes on the horizon (the Clinical Trials Regulation and the Data Protection Regulation) which could have a direct impact on the ability to conduct epidemic / pandemic research in the near future. Finally identification of potential supports to clinical staff critical to success of the project is required. Based on these issues some general and specific measures can be suggested at this early stage.

General Measures

A group of senior clinicians / researchers should be identified from with PREPARE to develop awareness and create some political momentum within both a) senior politicians or MEPs and b) public health officials amongst member states. Ideally this group would work in collaboration with colleagues in organizations with similar goals to PREPARE, for example, the WHO or ISARIC, to increase awareness of the potential public benefit of epidemic/pandemic research and help us inform policy. This group through working with these agencies could address the classification of the research from the outset which will directly impact many of the EARL issues downstream of this decision.

A working group should be established to develop and co-ordinate a public engagement campaign. In the first instance this group should identify key attitudinal and socio-cultural barriers that exist within and across the general public in member states in order to guide the potential impact and content of such a campaign. Ideally a unified media and engagement campaign can be

developed across Europe with core components addressing key areas of engagement in the project and its goals and individualized components reflecting an understanding and respect of area specific cultural factors which may influence potential recruitment into the study.

Centralized guidelines and agreement regarding allocation of resources are required to ensure cohesion of the research group and prevent some countries feeling disenfranchised due to particular EARL challenges they may face. This may include centralizing a fund for ethical approval thus preventing those countries in which this process is more laborious being "penalized" in terms of utilizing their grant allocation. Similarly explicit guidelines on what minimum proportion of grant must be allocated directly to research costs rather than to awards to institutions should be considered.

At a local level staff must be employed who have received central training (this may be via internet or centrally based workshops) in consenting and informing potential recruits and their families to improve the ability to develop meaningful and informative transactional consent and b) reduce the perceived additional burden on clinical staff. Ideally these research staff would be dedicated research staff who would not be redirected towards frontline clinical duties in the event of increased workload / staff shortages.

Specific measures with relation to ethics applications

Careful consideration must be given to the classification of each component of the study - quality improvement initiatives will be facilitated much easier across countries from both an ethics approval perspective and data protection understanding.

Guidelines for ethical submissions should include the requirements that are to be incorporated in the new EC Clinical Trials Regulation such as incorporating appropriate risk assessments evaluations in patient information leaflets, involvement of lay persons in development of protocols and streamlining processes for incident reporting. Working Package 1 will develop a working party to assess the potential PREPARE impact of this Regulation and ensure clear recommendations are included in protocol development and ethical submissions.

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