Priority needs for conducting pandemic-relevant clinical research with children in Europe: A consensus study with pediatric clinician-researchers

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Key words: children, infectious disease, outbreak, pandemic research, European Directive, Europe.

Funding: This work was funded by the European Union Seventh Framework Programme under the project ‘Platform foR European Preparedness Against (Re-) emerging Epidemics (PREPARE)’, (grant agreement 602525).

Abbreviated Title: Requirements for pandemic-relevant research in Europe.

Running Head Title: Pediatric pandemic research.

Disclosures: The authors have no conflicts of interest or funding to disclose.
ABSTRACT (max 250 words)

Background: Infectious disease pandemics (IDP) pose a considerable global threat and can disproportionately affect vulnerable populations including children. Pediatric clinical research in pandemics is essential to improve children’s healthcare and minimize risks of harm by interventions that lack an adequate evidence base for this population. The unique features of IDPs require consideration of special processes to facilitate clinical research. We aimed to obtain consensus on pediatric clinician-researchers’ perceptions of the priorities to feasibly conduct clinical pediatric pandemic research in Europe.

Methods: Mixed method study in 2 stages, recruiting pediatric clinician-researchers with experience of conducting pediatric infectious disease (ID) research in clinical settings in Europe. Stage one was an expert stakeholder workshop and interviews. Discussions focused on participant’s experience of conducting pediatric ID research and processes to facilitate pandemic research. Information informed stage two; an on-line consensus survey to identify pediatric clinician-researchers priorities to enable IDP research.

Results: Twenty-three pediatric clinician-researchers attended the workshop and thirty-nine completed the survey. Priorities were primarily focused on structural and operational requirements of research design and regulation: 1) Clarity within the European Clinical Trials Directive for pediatric pandemic research; 2) Simplified regulatory processes for research involving clinical samples and data; and 3) Improved relationships between regulatory bodies and researchers.

Conclusions: Results suggest that changes need to be made to the current regulatory environment to facilitate and improve pediatric research in the pandemic context. These findings can provide expert evidence to research policy decision makers and regulators and to develop a strategy to lobby for change.
INTRODUCTION

Infectious diseases with pandemic potential pose a considerable global threat. Clinical research is essential to ensure evidence-based public health responses and patient management in future infectious disease pandemics (IDPs). The unique nature of IDPs presents challenges to the conduct of research, as implementation must be rapid and potentially include multiple countries. Strategies to facilitate IDP research include fast track regulatory approval, pre-approved protocols, alternative consent models, novel trial designs and stakeholder engagement.

In considering IDP research, the populations that may be affected should be considered. For example, pandemic influenza can disproportionately affect different populations in comparison to seasonal influenza. During the 2009 (H1N1) pandemic, children, adolescents and younger adults had the highest burden of disease, and there were severe and fatal cases in children with no pre-existing risk factors.

While children and young people (YP) are an obvious and relevant group to include in clinical research they are frequently not recruited into trials. There may be a number of reasons for this including the perceptions that including them is difficult, that approvals may be subject to greater delay and some clinicians are reluctant to approach parents of sick children about research participation. However, families are generally willing to be approached about research even in stressful situations. Excluding children and YP from research has resulted in a lack of evidence for many medical interventions for this group and the practice to use off-label and unlicensed medicines guided only by clinicians’ experience and extrapolation of adult data.

There were few clinical research studies in the last influenza pandemics thus limiting the evidence base for improved care in the future. For example, following recommendations by organizations including the World Health Organization, Oseltamivir (Tamiflu) was widely...
stockpiled and prescribed during the 2009 H1N1 pandemic despite a lack of robust evidence on its efficacy and safety for this strain, and no clinical study was conducted during the outbreak to test this.(19) The aim of the EU-FP7 project ‘PREPARE, Platform for European Preparedness against (Re-) Emerging Epidemics’ (https://www.prepare-europe.eu) is to establish a research infrastructure to transform the research response to future IDPs and includes clinical observational and interventional studies recruiting YP and children.

We aimed to understand barriers and seek consensus on the priorities perceived by pediatric clinician-researchers in order to feasibly conduct pandemic-relevant pediatric clinical research in Europe. This is essential to inform pandemic study design and provide evidence for future European Commission policy and regulation.

METHODS

A mixed method study targeted at pediatric clinician researchers with experience of conducting pediatric ID research in Europe. Stage 1, aimed to identify challenges and priorities through a workshop and face-to-face interviews. Stage 2, was an on-line survey to establish consensus on priorities.

Ethical approval

Cardiff University School of Medicine Research Ethics Committee approved the study.

Recruitment

Stage 1, Workshop and interviews: Thirty-four clinician-researchers conducting pediatric research in Europe and attending the European Society for Pediatric Infectious Diseases (ESPID) conference, Leipzig (May 2015) were identified through the PREPARE consortium (https://www.prepare-europe.eu), invited by e-mail to participate in a 2-hour workshop and to
suggest additional people to invite. Those unable to attend were invited to an interview
during ESPID.

Stage 2, Consensus: Potential participants were identified by members of the Pediatric
European Network for the Treatment of AIDS and Infectious Diseases (PENTA-ID) network
(http://penta-id.org) and the PREPARE consortium. 85 pediatric clinician-researchers from
17 EU and EU-associated countries were invited by personal e-mail to participate (2016). Up
to three reminders were sent.

Data Collection

Stage 1. Workshop and interviews: A task and hypothetical scenario based topic guide was
developed to guide discussions around experience and perceptions of conducting pediatric ID
research and processes to facilitate IDP research. The scenarios focused on i) an adaptive
pediatric ID trial of licensed pharmacological interventions in an intensive care unit (ICU)
using deferred consent, and ii) an observational ID study using broad/waived consent to
access clinical data and surplus/additional clinical samples. Discussions were audio-recorded
and anonymised.

Stage 2. Consensus survey: Key priorities from stage 1 informed the survey. A data
collection website in the English language was developed using Survey Monkey. Data were
collected from 14th April to 25th August 2016. The survey comprised of 2 sections; i)
demographic information (country of work, experience of research and ID outbreaks), ii)
seventeen ‘research priority statements’ (with a short explanation). Participants were asked to
assign a rating score (1-5, with 5 being the highest and 1 the lowest) to how important they
thought each statement was to making pediatric pandemic research more feasible (national
and European level). An ‘I don’t know’ option was available. Free text comments and
additional priorities were invited.
Data Analysis

Stage 1. Workshop and interviews: Key thematic areas were identified as patterns in participant narratives that reflected areas to facilitate IDP research. Audio-recordings were analysed by two researchers in parallel. Findings were reviewed by participants for validation.

Stage 2. Consensus survey: Responses from all countries were combined. Data were analysed in two groups: i) priority at European level and ii) national level. As an a priori cut off, ratings of 4 and 5 were considered affirmative. Statements receiving affirmative ratings from ≥70% of participants would be considered to have achieved group consensus. Median and interquartile range, and frequency distribution were calculated. Comments and additional priorities were not included in the analysis but were considered for the discussion.

RESULTS

Stage 1. WORKSHOP AND INTERVIEWS

Participants

Pediatric researcher-clinicians from 10 countries (Estonia, Finland, Greece, Germany, Italy, Lithuania, the Netherlands, Spain, Switzerland, United Kingdom) attended the workshop (n=23) or participated in an interview (n=4) at ESPID. These included 24 participants who had received an initial e-mail invitation (70.6%). All participants had conducted pediatric ID research in hospital settings. 13 had worked during an ID pandemic or outbreak.

Key findings

Participants discussed their experiences of conducting pediatric clinical research within and across European countries. Some significant country differences were reported, however, many common challenges were highlighted. There was general agreement that alternative
approaches to conducting research are needed to conduct pediatric IDP research. Key
thematic discussion areas are provided in Table 1.

Table 1. Workshop and interviews: experience and perceptions of conducting pediatric
ID research.

Stage 2. CONSENSUS SURVEY

Participants
Pediatric clinician-researchers (n=39 (46% of those invited)) working in 15 countries
completed the survey (Table 2). 3 had also participated in the workshop. Respondents
completed all questions. 38 (95%) had experience of research in the last 5 years and 32 (80%)
had experience of working in an ID outbreak including influenza like illness (n=28 (70%)),
Ebola (n=4 (10%)), Dengue (n=1), SARS (n=1), Hanta virus (n=1), cholera (n=1), West Nile
virus (n=1) and other ID gastrointestinal outbreaks (n=3). Other experience included
laboratory research (n=17), research regulation (n=8) and social science research (n =2).

Table 2. Countries in which consensus respondents conducted the majority of their
work

Consensus
A single consensus round was conducted as all priorities exceeded the a-priori consensus
criteria. Results are given in Table 3.

Table 3. Priority to make pediatric epi/pandemic research more feasible at a National
and European level
Participants Additional Priorities

Additional priorities included open access publication, ensuring rapid pan-European availability of research data, laboratory standardisation, and the establishment of research networks.

DISCUSSION

IDP research that includes children and young people is essential to enable evidence-based healthcare for these populations. We identified pediatric clinician-researchers’ key priorities for facilitating this IDP research to provide evidence to research regulators and policy makers. Priority areas identified include clarity for IDP research within the European Clinical Trials Directive (Regulation), improving relationships between ethics committees and researchers, simplified regulatory processes for sharing data and clinical samples, coordinated networks for early identification of pathogens, consideration of alternative consent processes, pre-approved research protocols, improved stakeholder engagement and novel research design. These priorities are discussed below.

Provision of greater clarity within the European Clinical Trial Directive for both clinical trials applying low risk procedures and observational (non-interventional) IDP pediatric studies, was a key priority for pediatric clinician researchers. (The Clinical Trials Regulation superseded the Directive following this study’s data collection). The Regulation includes a definition for observational studies; however, it includes neither a legal framework for obtaining regulatory approvals for this type of research in different EU member states nor provides guidance specifically for pediatric research in the pandemic context. This omission, in addition to a potential lack of knowledge of the new framework and pediatric ethical issues among ethics committees will pose a considerable barrier to the implementation of multi-country IDP research.(20, 21). Lobbying European Commissioners for provision of greater
clarity for observational and low-risk interventional studies and including special 
consideration of pandemic pediatric research in the Regulation is essential to enable 
successful IDP studies that cannot be restricted by geographic boundaries.

A breakdown in the relationship between clinician researchers and ethics committees was 
highlighted in the workshop and consensus. This can result in delays of approvals and some 
countries being excluded from pediatric ID research. Recognition of a common purpose 
between regulatory bodies and researchers is essential for IDP research due to the need for 
rapid approvals and study set up. Solutions would include education of regulators around the 
unique nature of ID outbreak research, setting up designated ethical committees for IDP 
research and preparation of pre-approved IDP ‘sleeping’ protocols, which would be ‘ready to 
 implement’ as soon as a pandemic is officially declared. Sleeping protocols have been 
developed in the NIHR HTA pandemic portfolio and within the International Severe Acute 
Respiratory and Emerging Infection Consortium (ISARIC, https://isaric.tghn.org).(22, 23)

While the collection, storage and access to clinical data and samples are essential for 
observational IDP research, there are currently no regulatory provisions or shared collection 
resources in Europe to enable this. Even within countries, access and sharing of samples and 
data is often disparate and difficult. If routinely collected anonymised clinical data and excess 
samples could be made available for research, it would reduce the need for additional studies 
to collect these. Coordinating IDP research with Public Health Authorities (PHAs) 
(responsible for surveillance, collection of samples and associated research) could be key to 
enabling this, with reference to countries settings where these processes have been 
implemented. Engagement with PHAs and other stakeholders (e.g. public health policy 
makers) to develop a coordinated approach and strategy may need to be driven by an 
International research consortium like PREPARE. Wider consultation may need to include 
regulators, clinicians, patients, and members of the public to ensure understanding and
acceptability. Furthermore, embedding of research into routine clinical practice, availability of Biobanks and compliance with the 2018 General Data Protection Regulations must be considered in developing any strategy and plan to address this priority.

Linked to the above is the need for establishing national and pan-European networks and shared systems to rapidly identify new pathogens and outbreak cases. Delayed information sharing can lead to delays in outbreak identification. While specialist laboratories and surveillance systems exist, a European wide coordinated approach would be hard to achieve when even national implementation of shared systems was viewed as challenging in countries that have numerous healthcare systems. Alongside the set-up of shared systems, implementation of nationally agreed laboratory protocols is needed. Local laboratories may also not have the required technologies or expertise to identify new pathogens. In Australia a pediatric enhanced disease surveillance system has been established and this model may prove useful.(24)

Research recruitment is a further area for discussion. It could be argued that consent requirements for IDP research may not be equivalent to those operating in non-pandemic situations and models of consent require some consideration. Deferred and opt-out consent may provide ethically valid and useful models for some observational IDP research in the emergency setting for example where collection of clinical samples for research takes place at the same time as routine sample collection or if excess sample is used.(15, 21, 25)

Deferred consent is now included in the Clinical Trials Regulation, which is useful for some pandemic-relevant studies, however, there is some conflict in emergency situations.(21) Opt-out consent where study information is publicised at waiting room, hospital and ward level, is implemented in some countries for observational studies, but in others regulatory and data protection agencies do not permit this. Differences in parental consent requirements for IDP research may also complicate IDP research; currently in some countries only one parent must
sign, whereas in others both parents must give written consent. (26) This may be difficult if a parent is also incapacitated or unavailable in the case of a pandemic. While variable practice in consent requirements poses a challenge in emergency research situations, cultural factors in different European countries must also be carefully considered when aiming for more universally acceptable models. Acceptance and understanding of IDP research and consent scenarios is likely to require wide public education and engagement.

Stakeholder engagement, education and gaining trust are crucial for pediatric IDP research and again large ID research networks like PREPARE may be ideally placed to negotiate this. Stakeholders may include members of the public, politicians, the media and PHAs. While research to gain patient and public opinions about research has been conducted (27, 28) there is a clear need to extend this to pediatric relevant IDP research. A further need is to improve relationships and work more closely with government, as politicians were perceived as disinclined to trust scientific experts. Good media communication also becomes important as the media can influence public opinion of research potentially affecting decisions to participate in research. Closer working with public health agencies, which are among the first responders in a public health emergency such as an ID outbreak, may be critical for pandemic research.

Trial design will be crucial for the pandemic or IDP or outbreak scenario. Trials with outcome-adaptive randomisation may be ideally suited to the time-sensitive pandemic setting especially if these are set-up and ready to rapidly respond in the case of an outbreak or pandemic being declared. However these designs will also need to address some ethical concerns. (29, 30) Demonstrating parent and YP acceptability of this study design and providing information to ethics committees is key to avoid delays in approvals processes. In the workshop discussions, participants briefly indicated how they had overcome some of the challenges in their ID pediatric studies. It would be useful next step to gather these
scenarios in more detail to provide other researchers with knowledge of potential solutions and as evidence to facilitate regulatory approvals.

**STRENGTHS AND LIMITATIONS**

This study calls attention to a neglected area in pandemic-preparedness; pediatric clinical research. It reflects the viewpoint of pediatric clinician-researchers with experience of pediatric ID research in Europe and an understanding of IDP challenges. Most priorities were common to all participants and this commonality is a likely indication of generalisability of results to a wider group of pediatric clinician-researchers. Applicability of our initial findings to a broader group was confirmed by the survey results where the majority of respondents agreed on the priorities and proposed only a small number of additions.

Sources of potential bias are the identification of participants, the required response within a limited time frame and responder bias. Only participants attending ESPID were eligible for the workshops and interviews and it could be argued that our participants were not representative of all clinician-researchers. Our participants volunteered to participate and may have had particular experiences of problematic issues in conducting pediatric research. Therefore their views may be over-represented and not generalisable to a wider group.

There were some country specific differences that may be useful to explore in a subsequent study. Describing clear examples of innovative research practice applicable to IDP research would be valuable.

This study identified priority areas for change but did not develop a work plan or specific strategy for addressing each priority need.

**CONCLUSIONS**

Pediatric clinician-researchers perceived the need for key changes to facilitate pediatric IDP research. The study findings can be used to inform a strategy and action plan addressing the
priority needs, to provide expert evidence to International research policy decision makers, regulators and ethics committees and to lobby for changes.

ACKNOWLEDGEMENTS

We thank all study informants who contributed their time to this study. PREPARE is coordinated by Herman Goossens at the University of Antwerp. Further information about the work of PREPARE is available at http://www.prepare-europe.eu.

SOURCES OF FUNDING

This work was funded by the European Union Seventh Framework Programme under the project ‘Platform foR European Preparedness Against (Re-) emerging Epidemics (PREPARE)’, (grant agreement 602525).

AUTHORS CONTRIBUTIONS

MG, NAF, CCB and AN were involved in the funding application for the study. MG and NG co-led on study design and implementation, ethics approvals, participant recruitment, and analysis of workshop and interview data. MG led analysis of the survey data and is guarantor. MG, NG, NAF, KH, CCB, JB, PLF, MS, RM, PS and AN conceived the study idea. All authors contributed to study design and interpretation. AW administered the study, designed the survey tool and curated the survey data. MG drafted the manuscript and all authors provided critical review, edited and approved the final manuscript.

REFERENCES

Table 1: Workshop and interviews: experience and perceptions of conducting pediatric ID research.

<table>
<thead>
<tr>
<th>Discussion area: Regulatory approvals across Europe</th>
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</thead>
<tbody>
<tr>
<td><strong>Experience and perception:</strong></td>
</tr>
<tr>
<td>Increasingly difficult; increasing regulation, variability within and between countries, a lack of communication between regulatory bodies and discordance between ethics committees and researchers. Perceived solutions for IDP research might include pre-approved research protocols and a centralized and expedited approval system that is recognized by law in every European member state (though there may be problems with country acceptance). An example was provided where regional law had been amended (Spain) to allow observational research under a fast track approval process in a public health emergency (<a href="https://www.prepare-europe.eu/About-us/Workpackages/Workpackage-3">https://www.prepare-europe.eu/About-us/Workpackages/Workpackage-3</a>)</td>
</tr>
<tr>
<td><strong>Example quotes:</strong></td>
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<tr>
<td>“There is more and more legislation.. they (legislative bodies) don’t talk to each other or acknowledge each other.”</td>
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<td>“So much difference in the ethics permissions from committees for different centres …it is random and unpredictable….Some centralized approval and some de-centralized.”</td>
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<tr>
<td>“Even for a retrospective chart review we could not obtain ethical approval in Spain and Italy. We had to exclude them after a year of trying.”</td>
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<tr>
<td>“We never challenge at European level so it never gets better.”</td>
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<td>“…even if we get endorsement at EU level…this is not accepted at country level”</td>
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<table>
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<tr>
<th>Discussion area: Recruitment and alternative models of obtaining informed consent</th>
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<tr>
<td><strong>Experience and perception:</strong> Timely recruitment is essential for IDP research and deferred and opt-out consent for observational and low-risk intervention studies might be considered. Examples included opt-out consent where study information had been publicized at ward and hospital level (Greece, UK), and deferred consent for use pediatric blood samples (Spain, UK). In one Swiss centre, opt-out consent allowed clinical data and surplus clinical samples to be stored and accessed via an ethics application. In larger Netherlands hospitals, every patient needs to opt-out to prevent use of their anonymised data for observational research, and signatures are not needed. Acceptance of these consent models was seen as more problematic in some countries (Estonia, Holland, Austria, Germany). Two participants indicated that</td>
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</table>
obtaining prospective informed consent from parents should always be possible for IDs like influenza. Requirements for parental consent and child assent were also subject to country variability. Verbal consent was discussed and an example given where parental verbal consent was provided by telephone (Estonia).

Example quotes:

“It’s different in an epidemic (obtaining consent)….not equal to normal study consent when protecting a nation from epidemic disease.”

“It has (deferred consent)… has transformed our ability to recruit children quickly….moved recruitment from day three to day one which is meaningful for evidence.” (UK)

“Deferral is not right for an influenza trial, you have ten, fifteen minutes. For severe influenza there is time. Deferred consent is not needed and therefore not ethical.” (Netherlands)

“It (obtaining parental consent) is all about trust and communication.”

Discussion area: Simplified processes for collecting and sharing clinical samples and data

Experience and perception:

Using and sharing clinical data and samples is important for containing outbreaks and developing tests. While European public health authorities conduct surveillance, their authority to initiate and conduct research is variable. For example, in the UK, a pediatric surveillance scheme is in place and the Chief Medical Officer can initiate research (including observational pandemic research and studies assessing the safety or effectiveness of an existing intervention with an insubstantial evidence base) in the interest of public health under the heading of ‘clinical service evaluation’ without ethical approval or consent. Some participants indicated that in countries with a federal system of governance a countrywide response could not be coordinated in this way (Germany, Switzerland, Spain). In Spain, clinical samples for public health can be obtained under a consent waiver but this is not the case for obtaining research samples. Collection of anonymised samples and data for prospective research in Spain is possible where parent/guardians consent is provided, and these samples can be used for research under a fast track approval process (48 hours). In the Netherlands anonymised surplus clinical samples can be shared for diagnostic test validation. Participants highlighted data protection issues, particularly during the early stages of an outbreak where it might be easier to link data to individuals.
**Discussion area: Study design i.e. use of adaptive platform trial design**

**Experience and perception:**

Participants were positive about adaptive design platform trials for IDP research as an alternative to randomised controlled trials. They felt that the design mirrors the way patients usually receive clinical treatment and that this might be more acceptable to parents. While the design was not thought to impact recruitment negatively it was viewed as potentially difficult to explain to ethics committees.

**Example quotes:**

“It (Adaptive trial design) makes a lot of sense in a pandemic. We need to learn from an epidemic as it goes on.”

“It (adaptive design) might be more acceptable to parents.”

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**Discussion area: Stakeholder engagement and communication**

Wider engagement to facilitate understanding of IDP research is needed. Stakeholders included politicians, the media, parents and young people. Public health services (PHS) were perceived as being more politicized than clinical services; if they identified a research need during an outbreak, then this would be actioned by government, whereas clinical researchers do not have any means of influencing government to drive the IDP research agenda. At a European level, Ministers and Chief Scientific Officers were perceived to be increasingly risk averse and more likely to respond rapidly to societal influences. Clinician-researchers should be involved in government in decisions for outbreak research responses. They perceived a lack of trust in the independence of scientific experts at government level. Establishing better relationships with the media to positively report research and help gain public trust was seen as important. Participants also highlighted the need for better engagement with parents and young people (YP) to provide education and understand their views of around participating in IDP research, use of clinical samples and data, and consent models. This can be time consuming but should be possible for pre-approved protocols and would aid acceptability by ethics committees.

**Example quote:**

“Increasingly ministers are more risk averse. Politicians are younger and not used to dealing with a crisis...less prepared to wait and see...much more aware of societal influences. They don’t believe in independence of scientific experts...viewing scientific advice with suspicion... puts us in a fragile position.” (UK)
Discussion area: Recognizing the importance of pediatric pandemic research

Participants briefly discussed the evidence gap for pediatric clinical practice around IDs and the practice of using off-label antibiotic prescribing in these populations with parents generally being unaware of this.

Table 2. Countries in which consensus respondents conducted the majority of their work

<table>
<thead>
<tr>
<th>Country</th>
<th>Number</th>
<th>Country</th>
<th>Number</th>
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<th>Number</th>
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<tbody>
<tr>
<td>UK</td>
<td>7</td>
<td>Estonia</td>
<td>2</td>
<td>Romania</td>
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<tr>
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<td>Slovenia</td>
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<td>Finland</td>
<td>1</td>
<td>*Montenegro</td>
<td>1</td>
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<tr>
<td>Greece</td>
<td>3</td>
<td>France</td>
<td>1</td>
<td>*Switzerland</td>
<td>1</td>
</tr>
<tr>
<td>Belgium</td>
<td>2</td>
<td>Italy</td>
<td>1</td>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>2</td>
<td>Portugal</td>
<td>1</td>
<td>*Multiple countries</td>
<td>1</td>
</tr>
</tbody>
</table>

*Montenegro is included, as this country has started the process of accession to the EU. *Switzerland is included as an EU associated country and as research networks in Switzerland are included in PREPARE. *Participant stated that they worked in ‘multiple countries’ and did not provide a specific country of work.
Table 3. Priority to make pediatric epi/pandemic research more feasible at a National and European level

(median and interquartile range (IQR) for each rated statement)

<table>
<thead>
<tr>
<th>Area</th>
<th>No.</th>
<th>Area required to make pediatric epi/pandemic research more feasible at a National and European level</th>
<th>Priority at National Level (median and IQR)</th>
<th>Priority at European Level (median and IQR)</th>
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</thead>
<tbody>
<tr>
<td>EU Directive</td>
<td>1</td>
<td>Clarity within the new clinical trials Directive for epi/pandemic observational research including children</td>
<td>5.00 (5.00-4.00)</td>
<td>5.00 (5.00-4.00)</td>
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<tr>
<td></td>
<td>2</td>
<td>Clarity within the new clinical trials Directive for epi/pandemic clinical trials including children</td>
<td>5.00 (5.00-4.00)</td>
<td>5.00 (5.00-4.00)</td>
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<tr>
<td>Regulatory processes</td>
<td>3</td>
<td>Recognition of a common purpose and improved relationship between regulatory bodies, ethics committees and researchers</td>
<td>5.00 (5.00-4.00)</td>
<td>5.00 (5.00-4.00)</td>
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<tr>
<td></td>
<td>4</td>
<td>Simplified regulatory processes for observational research involving collection, use and sharing of anonymised clinical data (relevant to infectious disease epi/pandemics).</td>
<td>5.00 (5.00-4.00)</td>
<td>5.00 (5.00-4.00)</td>
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<tr>
<td></td>
<td>5</td>
<td>Simplified regulatory processes for research involving the collecting, using and sharing of anonymised surplus clinical samples (relevant to infectious disease epi/pandemics).</td>
<td>5.00 (5.00-4.00)</td>
<td>5.00 (5.00-3.25)</td>
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<td>Pre-approved protocols</td>
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<td>5.00-4.00</td>
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<tr>
<td>Alternative consent models</td>
<td>7</td>
<td>Regulatory approval of alternative models of obtaining patient informed consent for research involving the use of clinical data in an epi/pandemic</td>
<td>4.00</td>
<td>4.00</td>
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<td></td>
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<td>5.00-4.00</td>
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<td>8</td>
<td>Coordinated processes for the early identification of potential new outbreak cases and pathogens</td>
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<td>9</td>
<td>Regulatory approval of alternative models of obtaining patient informed consent for research involving the use of clinical samples (excluding genetic testing) in an epi/pandemic (e.g. deferred consent, opt-out consent, and alternatives to written consent).</td>
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<td>10</td>
<td>Regulatory approval of alternative models of obtaining patient informed consent for ‘low risk’ research trials (e.g. comparative effectiveness) in an epi/pandemic (e.g. deferred consent, opt-out consent, and alternatives to written consent).</td>
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<td>11</td>
<td>Regulatory approval of alternative models of obtaining patient informed consent for ‘high risk’ research trials (e.g. novel agent) in an epi/pandemic (e.g. deferred consent, opt-out consent, and alternatives to written consent).</td>
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<td>Adaptive trial design</td>
<td>13</td>
<td>Recognition of the benefits of novel trial designs e.g. adaptive platform trials by regulatory and ethics committees</td>
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<tr>
<td>Communication and trust</td>
<td>14</td>
<td>Good two-way communicating between researchers and senior government regarding research requirements for emerging infectious disease outbreaks</td>
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<td></td>
<td>Establishing trust between researchers and senior government regarding research requirements for emerging infectious disease outbreaks</td>
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<td>15</td>
<td>A strategy for engagement and good communications with the media to aid positive reporting of research for IDPs including children</td>
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<td>16</td>
<td>Parent and young person engagement and education about epi/pandemic research</td>
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<td>Training</td>
<td>Training of front-line clinical staff in the procedures of pre-approved protocols for epi/pandemic research</td>
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^Not asked to discriminate between National and European level