Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

Perpetual observational studies: new strategies to support efficient implementation of observational studies and randomized trials in infectious diseases

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Background

Emerging infectious diseases are a growing threat, through population growth, increased trade and travel, urbanization, deforestation, and climate change [1]. Clinical research in response to emerging infectious diseases is challenging; selecting and contracting the appropriate study sites for a trial is time consuming, and often too few patients can be timely recruited to acquire high-quality evidence about the best treatment strategies [2]. In 2014, the EU-funded PREPARE project (Platform foR European Preparedness Against (Re-)emerging Epidemics) was initiated to rapidly respond to severe infectious diseases outbreaks. It initiated two adaptive platform trials, the REMAP-CAP [3] and the ALIC4E trial [4], determining the effectiveness of multiple treatment strategies for a single disease. The REMAP-CAP trial was designed for a pandemic of severe community-acquired pneumonia and expanded globally during the COVID-19 pandemic. It has already delivered 10 important conclusions for better treatment of COVID-19 [3].

Antimicrobial resistance (AMR), on the other hand, is a more silent pandemic, which further augments the burden of infectious diseases. Development of new antibacterial agents has slowed, due to a combination of low return on investment and challenging

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clinical trial conditions [5]. Since the 2000s, national and global efforts have been initiated to promote antibiotic development, including the setup of public–private partnerships, like COMBACTE (Combatting Bacterial Resistance in Europe), funded by the EU's Innovative Medicines Initiative. Since 2013, COMBACTE has focused on rapid and efficient development of new AMR prevention and treatment strategies, through site selection streamlining, real world data collection for patient enrichment and pathogen prioritization [6], and improvement of clinical trial efficiency through innovative methodological and statistical approaches [7].

A clinical research network applying different innovative concepts could enhance research efficiency to address both the growing threat of (re-)emerging infectious diseases and the increasing burden of AMR. Therefore, the academic partners from PREPARE, COMBACTE, and other EU-funded collaborative networks (see Acknowledgements) combined their strengths to establish the European Clinical Research Alliance on Infectious Diseases (Ecraid) Foundation in January 2022—a clinical research network that aims to efficiently generate rigorous evidence to improve the diagnosis, prevention, and treatment of infections in Europe through innovative solutions. Here we discuss the advantages and challenges of the implementation of Perpetual Observational Studies (POS).

Methods to improve implementation efficiency of observational studies and randomized trials

Various methods have been applied to improve the efficiency of clinical research. Clinical research networks have been set up to improve research infrastructure; they provide essential resources to clinical researchers, including specialist training, information systems, administrative services, and communications expertise. The application of a master protocol takes efficiency one step further; within a research infrastructure, a common protocol is applied to simultaneously coordinate multiple randomized controlled trials (RCTs) [8]. This structure can answer questions on one or more interventions in multiple diseases (basket trial) or multiple interventions in a single disease (umbrella or platform trial) [8]. In the latter case, the umbrella trials stratify patients into subgroups based on (molecular) markers and assign them to fixed treatment arms, whereas the platform trials have dynamic treatment arm assignment for a single indication [8]. RCTs can also be conducted within longitudinal epidemiological cohorts or within existing registries. In Trials Within Cohorts, or cohort-multiple RCTs, cohort participants consent to contribute control data to future unspecified trials at recruitment. Trial-specific consent is only requested from those participants randomly allocated to an intervention arm [9]. A POS combines important aspects of these different strategies; it is based in a research infrastructure, applies a core protocol, and entails a prospective cohort for epidemiological purposes. However, the POS research infrastructure has a broader focus (infectious diseases), its core protocol is more flexible, and, in contrast to Trials Within Cohorts, the POS can host multiple observational studies and RCTs in parallel (Table 1).

What is a perpetual observational study?

A POS is a prospective, observational clinical study enrolling patients on a perpetual basis, collecting a set of demographics, clinical characteristics, and outcomes, mostly available through routine care, as described in a core protocol. The POS in Ecraid are multicentre studies designed to address key clinical research gaps, including variations in clinical practices, incidence of infectious disease syndromes, and associated risk factors. Each core protocol establishes the general observational cohort and can be extended with appendices for more specific observational or interventional studies. Naturally, such 'add-on' studies would require resubmission for ethical and/or regulatory approval. Thus, each POS creates a clinical research backbone, ready to concurrently or sequentially embed studies (observational, experimental, investigator-initiated, or commercial) and efficiently advance the evidence base for infectious diseases management. Within Ecraid, we have initiated five POS, recruiting patients in study sites across Europe, which target five strategically chosen infectious syndromes in hospital and community care settings (Table 2).

What are the challenges and advantages of a perpetual observational study within a clinical research network?

Using the POS within a clinical research network, the i) quality, ii) planning, and iii) efficiency of experimental or observational multicentre studies can be improved compared to conventional initiatives. i) Training and regular feedback improves data quality, creating a network of sites with experienced Principal Investigators and Good Clinical Practice–certified personnel.

ii) For study planning, the POS collects empirical data, such as recruitment rates and cumulative incidence of endpoints of interest, which can: 1) help determine the feasibility of new studies within the domain and fine tune their design; 2) improve site selection for studies, especially for studies focused on specific pathogens or resistance traits; 3) inform sample-size calculations and timelines for embedded studies; and 4) assess the feasibility and/or added value of implementing adaptive designs through empirically informed simulations.

iii) The efficiency of embedded, multicentre studies can be improved through shortened timelines for site contracting and study initiation via established professional relationships. Ethical and regulatory approvals can be expediated, as already approved documents can serve as templates for embedded studies.

The POS can also have other benefits. The clinical outcomes collected within the POS can be used for real-world data collection on newly registered drugs and vaccines. The POS data from the full network can be used to assess external generalizability of RCT results, often based on a selective patient sample. A biobank of biological samples collected within the POS can provide a unique opportunity to study rare pathogens or resistance patterns. It takes research preparedness a step further, as the POS preemptively collects data that can promptly address arising research questions due to outbreaks, emerging infectious diseases, or pathogen variants. The clinical and epidemiological data can further serve to provide high-quality burden assessments for infectious syndromes, improving reliability and representativeness of existing estimates. Since the POS are integrated within a clinical research infrastructure, different additional services could be offered. Within Ecraid, expertise will be available for site selection (CLIN-Net and the Primary Care Network selection team), microbiology (LAB-Net), epidemiology (EPI-Net), and statistical methods (STAT-Net), depending on requirements of external study teams.

Data harmonization and data sharing

Data harmonization and data sharing are paramount for an effective clinical research network. This can be facilitated by standardized data collection in line with Clinical Data Acquisition Standards Harmonization principles [10], as well as through the harmonization of diagnostics, treatment, and follow-up procedures across clinical centres participating in the network. Finally, automated data collection through electronic health records could

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Table 1
Advantages and challenges of different approaches that could improve efficiency of RCT implementation

Approach	Description	Advantages	Challenges
Master protocol: Basket trial	RCT with one fixed treatment arm focused on multiple diseases or disease subtypes with the same molecular profile (mostly in oncology)	- Enables RCTs for rare diseases - More efficient; can investigate multiple rare diseases within one RCT based on one master protocol	- Stratification and control per disease type is still required - Challenging to select an endpoint, which is informative for all strata - Limited to one treatment
Master protocol: Umbrella trial	RCT with multiple treatment arms for one disease, with subgroups based on (molecular) markers	- More efficient; can study multiple treatments within one RCT based on one master protocol and uses one shared control arm	- Very challenging for pivotal trials; not easily accepted by regulatory authorities, collaboration of different pharmaceutical companies is required
Master protocol: Platform trial	RCT with multiple, dynamic treatment arms (in multiple domains) that can be dropped based on accumulating evidence, or added based on novel developments	- As above, more efficient - Can minimize patients randomized to inferior treatment - Very flexible	- As above, challenging for pivotal trials - Complex planning and implementation - Possible influence of temporal trends that needs to be acknowledged
Registry based RCT	Patient parts of a registry are randomized, after which documentation of treatment and/or outcomes occurs in the preexisting registry with outcome measurements at routine care time points	- Efficient; limited interventions and follow-up outside of standard care - High data quality through trained physicians - Harmonized data through application of standardized definitions - Less restrictive inclusion criteria; higher external validity - Detailed information about nonparticipants - Data available to inform design and sample size	- Only possible for syndromes in settings with existing registries - Little flexibility with regards to data collected, time of visits, or endpoint selection
Trial within cohort, cohort multiple RCT	Implementation of RCTs in existing disease-specific cohorts, with informed consent only for patients randomized to the experimental treatment arm	- Similar to registry-based RCT - Delayed informed consent for the treatment arm only, can reduce attrition and disappointment bias	- Disease-specific cohort needs to be established - Standard treatment needs to be an acceptable comparator - Nonresponse in patients refusing participation in treatment arm - Important risk of crossover from intervention to control arm
Perpetual observational study within a clinical research infrastructure	Network of study sites running a perpetual observational study based on a minimal protocol, ready for embedding observational studies or RCTs	- Data available to inform centre selection, study design, and sample size - Very flexible, additional data requirements can be implemented - High data quality through trained personnel - Harmonizated data through application of standardized definitions across study sites - Information available about non-participants - Procedures and templates in place for site contracting and ethical approval - Services available (site selection, microbiological, epidemiological, and statistical expertise)	- Organization of multiple parallel studies in the same network - Motivation of participating sites - Sustainability; Externally funded research activities need proper margins to sustain the POS activities - Theoretical efficiency gains still need to be assessed in practice

POS, perpetual observational study; RCT, randomized controlled trial.

further enhance standardization, data quality, and research efficiency, supporting long-term sustainability of the network. All of these elements will be explored in the Ecraid-POS.

Informed consent

Because the POS are observational in nature, pose no risk to participants, and serve a public benefit, a waiver of consent or opt-out procedure would be acceptable to many ethical committees. However, within ECRAID-Base, it was decided to apply informed consent for all patients to optimize the POS benefits. It will ensure that the POS data, like recruitment rates or frequency of clinical outcomes, will be more representative for future embedded RCTs, with an obligation of informed consent. It will also result in the continuous training of patient recruitment and informed consent procedures, which will maximize enrolment of eligible patients in future embedded RCTs. Moreover, the reuse of data and/or clinical samples is integral to the POS concept, for which broad consent for future use through an informed consent procedure is the preferred approach. Finally, the application of informed consent could improve reliability of postdischarge follow-up. However, informed consent also entails risk of bias related to nonparticipation and loss-to-follow-up due to consent withdrawal. The data from electronic medical records and the POS itself could be used to better understand and quantify this possible bias and inform mitigation strategies.

Challenges

As the POS approach is new, careful explanation of the benefits, ethical issues, and quality safeguards will be necessary. Although efficiency gains are expected, the speed of regulatory and ethical procedures will depend on the preparedness of ethical committees and regulatory authorities to facilitate these processes. Then, not all potential study sites may have the capacity to take on new, long-term studies, but the pool of possible study sites across Europe should be large enough to set up efficacious POS networks.

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Table 2
Description of the five perpetual observational studies initiated within the European Clinical Research Alliance on Infectious Diseases

Name	Infectious syndrome	Healthcare setting	No. of anticipated sites	No. of anticipated patients, per y	Description
POS-ICU-VAP	Ventilator-associated pneumonia	Intensive care unit	40	4000	A platform for observational and randomized studies in the domains of VAP prevention, diagnosis, and treatment. Its primary endpoint is focused on study quality and efficiency, whereas its secondary endpoints focus on VAP epidemiology. Data collected in the POS will provide the information necessary for the design of any study in this field with regards to incidence and microbiological etiology of VAP and VAP outcomes, including clinical or microbiological cure, duration of mechanical ventilation, and mortality.
POS–cUTI	Complicated urinary tract infection	Hospital	40	3000	A platform for rapidly implementing randomized studies focusing on cUTI. The POS will allow a continuous evaluation of best practices related to patient enrolment and data collection to improve study execution. It will also facilitate the harmonization of local practices in diagnosing and treating cUTI across study sites. The collection of clinical information will further support design of innovative clinical trials, including population enrichment.
POS-ER-ARI	Community-acquired acute respiratory tract infection	Secondary Care	40	4000	This POS will be implemented in clinical networks that were active in PREPARE observational studies. It will provide an infrastructure capable of rapidly implementing clinical trials, related to the treatment of ARI. The POS will also answer key clinical questions on ARI (e.g the effectiveness of different established diagnostic and therapeutic practices on clinical outcomes, and description of the burden of ARI presenting acutely to hospitals).
POS-PC-ARI	Community-acquired acute respiratory tract infection	Primary care	50–100	2000 registered, of which 400 included	This POS will be implemented in the Ecraid primary care research and PENTA networks. The PENTA sites will be recruiting children presenting to hospital-associated and out-of-hours care settings. Presentation and management details (diagnostics, prescribed medication) will be anonymously registered, with a subset of patients selected for capturing microbiological and outcome data. As a precursor to the POS, a point-prevalence audit survey was rolled out before (and three times during) the COVID-19 pandemic, showing this POS may become a valuable tool to capture shifts in patient management due to changing circumstances.
POS-ER-Disease X	Infectious disease syndromes among immunocompromised patients admitted to hospital	Hospital	5–8	400	This POS aims to study febrile illness among immunocompromised adult patients admitted to the hospital with unknown or unusual viral aetiology. The network facilitates alignment of local practices of laboratory diagnosis among participating sites and provides an infrastructure to evaluate novel diagnostic tools (i.e. metagenomics).

POS, perpetual observational study; VAP, ventilator-associated pneumonia; cUTI, complicated urinary tract infection; ARI, acute respiratory infection: ER, emergency room; PREPARE, Platform foR European Preparedness Against (Re-) emerging Epidemics; RECOVER, Rapid European SARS-CoV-2 Emergency Research response; PC, primary care; PENTA, Paediatric European Network for Treatment of AIDS.

Moreover, POS focused on different infectious diseases can be run in parallel at the same site. Study site selection should be a transparent process, and participation in a POS should not limit a study site from participating in other research activities. Because a large pool of centres will be reporting data, data standardization will require detailed protocols, intensive training of sites, and active data monitoring. Selection bias associated with informed consent will have to be monitored as well. Finally, demonstration of the benefits of POS will be required to keep researchers, sites, and funders engaged and to ensure long-term research sustainability.

Conclusions

The risk of (re-)emerging infectious diseases and the increasing prevalence of AMR requires a proactive stance to support efficient implementation of high-quality observational and interventional studies to better manage these health threats. The implementation of disease-specific POS within a clinical research network can improve the planning, quality, and efficiency of multicentre studies and has the potential to shape the future of clinical research, although real-life benefits will need to be established. In Ecraid, five syndrome-specific POS are initiated that focus on VAP, cUTI, ARI in primary and secondary care, and unexplained severe infectious syndromes, which will provide important insights into the challenges and advantages of POS.

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Author contributions

MdK conceptualized and supervised writing of the commentary. NHK, HvW, TJ, JD, and MdK drafted the manuscript and created the tables. All authors contributed to Table 2, reviewed and edited the commentary and accepted the final version.

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