Australian Clinical Trials Alliance

Exploring Technologies to improve recruitment

Scoping review

September 2022

ACTA gratefully acknowledges operational funding from the Australian Government's Medical Research Future Fund

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Document History

Version	Date	Changes made to document	Author
1.0	15 September 2022	First version	HB
1.1	7 October 2022	Requested edits (minor)	HB
1.2	10 January 2023	Edits on technology categories	HB

Workstream 4 – Making trials more efficient and easier

Activity 4.5 – Explore technologies to improve recruitment

Introduction

The COVID-19 pandemic has accelerated digitization and technology advancement in clinical trial conduct, in addition to the roll-out of decentralised clinical trials (DCTs) that support hybrid models of participant recruitment. Technological innovations offer the potential to improve efficiency and productivity through the use of novel tools that increase patient engagement, reduce patient burden, and improve trial management.[1] Yet the expanded use of new technologies also raises regulatory, operational, and usability concerns and face barriers to implementation.[1] The use of technology can be especially useful when there are logistical constraints such as lengthy and frequent travel required to study sites, and financial constraints such as costs to attend required appointments for participation in clinical trials. Additionally, technology can be used to search existing digital documents and data repositories, even in unstructured, data formats such as medical records.[2] This has the potential to not only increase recruitment in rural/regional/remote areas, but also expand recruitment to underrepresented groups (including culturally and linguistically diverse groups) and those with rare diseases.

Many issues influence recruitment, and they can be classified as participant-, physician-, trial- or protocol-related, or 'other' factors.[3] Recently, a local study identified challenges associated with participant recruitment in Australia to include protocol variables (inclusion/exclusion criteria being too stringent), site capabilities and resources (insufficient resources, lengthy time for ethics/governance reviews, competing site priorities, lack of site accountability), and participant related barriers (onerous visit schedules, complexity of PICFs, inequity in access to participants in rural/remote areas).[4] Australia's relatively small population itself can be a recruitment barrier, particularly in therapeutic areas where there is competition for the same participant population.[4]

Failure of recruitment mechanisms is also one of the key factors for unsuccessful clinical trials, which may lack the technical infrastructure needed to cope with the complexity of running a trial, including the absence of reliable and efficient adherence control, patient monitoring, and clinical endpoint detection systems.[5] While it is imperative to not only engage patients and consumers on the availability of different clinical trials for participation through different methods such as through doctors, social media, clinical trial registries or online websites (hospital, research provider or study specific),[4] it is also essential that the appropriate use of technologies enable both recruitment and retention of these patients and consumers for their benefit as well as the cost of replacing participants during the course of a clinical trial. Artificial intelligence (AI) may help overcome recruitment failures, especially using machine learning (ML) and deep learning (DL), which can find patterns of meaning in large datasets such as text, speech, or images, being of particular interest. Natural language processing (NLP), another form of AI, may be utilised to understand and correlate content in written or spoken language, and these mechanisms may be used to correlate EHRs to improve patient-trial matching and recruitment.[5]

Although there are no readily available quantifiable metrics describing patient perspectives on the value of participating in clinical trials in Australia, the Pharmaceutical Society of Australia (PSA) has suggested that raising awareness about clinical trials with patients, families, and the public is essential.[6] This is not only to encourage and improve patient participation in trials, but to improve the value of clinical trials generally. Metrics such as the proportion of Australian adults participating in oncology clinical trials compared with the UK appears to indicate that fewer Australians participate in such studies but this is hard to interpret as there is no detail about the nature of the trials (e.g. phase, type of intervention etc), or the patient populations involved.[7] Additionally, the average number of participants per trial site in Australia is generally low, relative to Canada which has a similar population density.[8] There is no simple way to obtain this information at present and it is currently impossible to know the reasons if indeed rates of participation are lower. However, some initiatives, such as the Research4Me Think Tank[9] and Thank You Sessions by the White Coats Foundation,[10] are designed to raise awareness of clinical trials amongst consumers and have demonstrated that patients are interested and willing to participate in clinical trials. Finding information about clinical trials that may be relevant and that are available to consumers is still a barrier to

participating in trials[8, 9] and may provide one (of the many) reasons behind low participation rates in clinical trials in Australia. Most clinical trials in Australia also exclude non-English speaking members of the community through exclusion/inclusion criteria.[11] This is an obvious structural barrier to participation for underrepresented communities and clearly affects the generalisability of trial outcomes and results. It illustrates just one way in which improving participation in clinical trials could be achieved. More importantly, it indicates that there is a need to engage with a diverse representation of the Australian population such as CALD members and Aboriginal and Torres Strait Islanders in the design of trials to ensure that there is no structural exclusion inherent in the design of the trial itself that creates barriers to participation.

A recent report by an existing technological recruitment platform reported that an astounding 80% of clinical trials struggle with enrolment, with a 30% drop out rate once a participant has signed up for a trial.[12] This highlights the importance of creating participant centric trials which consider participant burden including literacy gaps between researchers and patients, restrictions and inconvenience to patients with pre-existing health conditions, all of which may ultimately affect participants' decisions to participate in clinical research.

Electronic health records (EHRs) provide additional opportunities to enhance patient care, embed performance measures in routine clinical practice, and facilitate clinical research.[13] Utilising EHRs for clinical trial recruitment offers multiple opportunities to advance clinical care. Internationally, there is an increased focus on EHRs data aggregation to allow selection of trial participants o*r outcome assessment to support trials*, particular in the US and Canada.[14] Utilising EHR for research may be more effective in countries with more centralised healthcare data systems; in fact use of the EHR for clinical trial patient recruitment is more common than other strategies in some European countries, the UK and the US.[13-15] EHRs may potentially be used to assess study feasibility, to facilitate patient recruitment, and streamline data collection at baseline and follow-up.[4] In addition, the EHR is the main source for patient recruitment for Nordic Countries, including Sweden, Norway, Denmark, and Finland.[16] However, these countries have comprehensive healthcare data sources with national population coverage and appear to use the EHR for recruitment more so than other European countries.[16] In the UK, longer-term interoperable EHR systems providing simple access to up-to-date datasets to facilitate trials is still too early in development to be used effectively for patient recruitment.[15]

Ensuring data security and privacy, ethical considerations, data standardization, overcoming the challenges associated with linking diverse systems and maintaining infrastructure for repeat use of high-quality data, are some of the challenges associated with using EHRs in clinical research.[13,14] Collaboration between academia, industry, regulatory bodies, policy makers, patients, and electronic health record vendors is critical for the greater use of electronic health records in clinical research.[13]

Recently, there has been a shift towards alternative clinical trial recruitment sites such as pharmacies as they are more likely to capture rural/remote/regional patients.[17,18] Identifying patients for clinical trial recruitment through primary care (including pharmacies) has had traction in countries like the Unites States where pharmacy chains are in the process of determining which aspects of clinical trials can be performed virtually with patients at home, as well as which aspects can be done in a pharmacy.[18] It is widely recognised that community practitioners like general practitioners (GPs) and pharmacists see a larger group of patients in the community as well as offer basic health procedures; hence they may play a key role in future clinical trial recruitment.

Advances in digital technologies, patient opt-in solutions, EMR funnels, and community site-based data analytics are making it easier for sponsors and CROs to find, evaluate and recruit patients from a wide geographical area without the need for the patient to visit a trial site.[18] Internationally, the most effective digital tools widely utilised for finding potential participants in clinical trials in the UK include (i) database-screening tools such as the Clinical Practice Research Datalink (CPRD) which contains EHR data from GP clinics all over the UK, (ii) in-house built tools and (iii) disease registries.[19] Software/apps and named online services (e.g. Quintet) are less utilised for recruitment in the UK.[19] In addition, a priority in the 2021-2025 European Union Commission is the creation of a European Health Data Space to promote better use of health data, including EHR data for research.

In the US, data mining of the EHR,[20] such as collating patient electronic health data from multiple disparate data sources into a cancer repository[21] is commonly utilised for clinical trial recruitment. Some platforms that match clinical trials with patients through machine learning have been developed in the US, including Watson for Clinical

Trial Matching (IBM) Corp, Deep 6 AI (artificial intelligence), Synergy Innovation, Smart Patients, Antidote Technologies and Mendel, which have a high sensitivity and specificity for eligibility identification for clinical trial enrolment.[20] Other technologies used for recruitment in the US include automated alerts (notification to clinicians or research staff of potentially eligible clinical trial patients through software platforms) and natural language processing (NLP).[20] On the other hand, digital technology such as using smartphones are better utilised for patient retention rather than recruitment in the US[21] and UK,[17] such as smartphone reminders used for sending clinical reminders, and monitoring symptoms.

Similar to the challenges associated with EHRs, the main challenges for implementing these technologies are security, transparency of data (risk of data breach etc), ensuring equitable and representable patient recruitment,[19] costs[20] and EMR data sharing with researchers,[20,21] including legislative restraints to use of the EHR for recruitment.[22]

Currently, there are multiple technological platforms in Australia working to: 1) increase visibility of clinical trials to participants (participants search/are matched for clinical trials and enrol, giving their information to be contacted for eligible trials) including referral systems through primary or specialist care providers, 2) use digital technology to find eligible participants for clinical trials through integrated AI, use of in-house build technologies for recruitment, and use electronic medical records (suitable for places with centralised medical records), 3) use of software to develop NLP models and integrate into stand-alone medical systems to allow trialists to find potential participants for clinical trials with ease and more accuracy (subject to how accurate, integrated and real-time the data are, these may be more suitable for chronic rather than acute conditions). While data mining can help to find eligible, informed, and motivated patients, NLP can translate complex terminology used in clinical trials eligibility criteria into simpler terms, making it more accessible and easy to understand to prospective patients.[22]

The use of AI has been incorporated in both the digitisation space as well as the use of software to convert unstructured medical data from multiple sources into a more consistent and translatable format, allowing for targeted data mining. The use of AI can be optimised via universal data management and reduction of bias in data, which can be a limiting factor during trial recruitment. Artificial intelligence is also increasingly being used in the digital space interacting with patients particularly in clinical trials space, as a tool to convert trial protocol summaries with complex language into simpler, easier to read and more comprehensive information in order to bridge the gap between researchers and potential trial participants to greatly aid recruitment.[12]

Multi-trial matching can also be achieved by leveraging AI and machine learning.[23] An integrated clinical trial management solution (CTMS) can prioritize communications between patients, sponsors, CROs, and sites, and help drive the future of clinical research. Real-time centralised data with multiple smart features like mobile configurability, globally apt features, scalability and ease of use are made easy with an integrated CTMS[24] and this can assist in both recruitment and retention of patients in clinical trials.

In addition, there has been an increase in the visibility of the benefit of using clinical quality registries (CQRs) to identify suitable clinical trial participants with minimal cost and minimal ethics/governance barriers, particularly relevant in the Australian setting where multiple state and jurisdictional legislative differences exist for the collection and sharing of patient medical data. In Australia, there has been substantial success in establishing clinical quality registries, and it is hoped that as we move forward, the utility of accessing clinical registries in the recruitment of patients into clinical trials can be maximized. A recent Australian study has shown that 47.3% of potential clinical trial participants would prefer to be made aware of a clinical trial through clinical trial registries.[4] Some CQRs that are currently being used for patient recruitment in Australia include The Global Angelman Registry for Angelman Disease,[25] The MiND AUS Registry for MND patients in Australia,[26] and JoinUs (The George Institute, Australia).[27]

Although there are currently at least 20 registry-based trials being conducted in Australia, the potential of CQRs as clinical infrastructure is greatly underutilised, partly due to there being no agreed approach or standardised method to undertake registry-based trials and partly because of the lack of sustainable funding to support such CQRs in the long term.[28] Both Europe and the US have made progress in identifying these issues and have developed guidelines and policies on the utilisation of clinical registries for research.[28] In the US particularly, many types of registries have been used to successfully recruit patients for numerous clinical trials, the most frequently being cancer

registries.[29] To further increase registry-based clinical trials, The Clinical Trials Transformative Initiative (CTTI) has provided a set of recommendations that helps researchers determine the suitability of an existing registry (or when designing a new registry) to conduct a registry-based clinical trial.[30] Some of these guidelines and recommendations could be adapted for the Australian clinical trial landscape.

To improve the capability of CQRs for research in Australia, researchers, regulators, and consumers need to demonstrate to research funding bodies the need for better CQR utilisation for recruitment of clinical trial patients, what interventions are appropriate for patients recruited from CQRs and the associated time and cost benefits of registry-based trials. The use of technology to better incorporate recruitment of patients into clinical trials from CQRs needs to be fully utilised, as this space offers a promising recruitment strategy into clinical trials, particularly in disease areas with established CQRs.

More recently, the proposed National Front Door concept in Australia is aiming to make it easier for patients, researchers, industry representatives and sponsors to find, conduct, participate and invest in high-quality and ethical research in Australia, including clinical trial research.[31] This would target creation of a single national streamlined and interconnected platform in collaboration with all jurisdictions to enable a sustainable place for real-time and accurate information regarding clinical trial activity and site capability. Options for improving research participation through a related recruitment portal, the National Clinical Trials Front Door, will also be considered, which will include mechanisms that facilitate access to third-party participant recruitment providers.[31] However, the success of this platform will depend on multiple factors, including the ability to deliver this comprehensive platform in the near future to address the current real-time problems in recruitment.

A recently developed systematic map which identified comparative studies of digital tools for recruiting and/or retaining participants in health RCTs nationally has been reported. This study identified that the most frequently studied digital tools were social media, internet sites, email and tv/radio for recruitment and email and text-messaging for retention.[32] While there is limited evidence on the efficiency of digital tools and their impact on RCT participants and investigators,[32] a recent systematic review identified that targeting potential participants using online remedies is an effective approach for patient recruitment for clinical research.[33] Online recruitment was both superior in regard to time efficiency and cost-effectiveness compared with offline recruitment which outperformed online recruitment with respect to conversion rate. Nevertheless, it may be worthwhile identifying a framework to evaluate such technologies. There is a need to identify criteria to evaluate the efficiency or capability and limitations of such technology in the future. In addition, organisations have different capabilities and priorities, and identifying which technology is most appropriate is also an important consideration. Centralised guidance frameworks, such as the GREET Clinical Trial Site Recruitment Guide, may also help organisations better recruit, and retain patients through assessing study feasibility, better planning, and keeping the participants front of mind.[4,34]

Analysis of existing capabilities

We've identified the following technologies currently being utilised to improve patient recruitment into clinical trials, and have categorised them into four main categories*:

Name of technology	Register	Artificial Intelligence	Platform / Framework	Other	Use in Australia
Victorian Cancer Trials Link[35]	✓				✓
Australian Cancer Trials - ANZCTR[36]	✓				✓
JoinUs Register[27]	✓				✓
ClinTrials.gov[37]	✓				✓ (US based)
StepUP for Dementia Research[38]	✓				✓
Can Refer NSW & ACT[39]	✓				✓
Health Match[40]	✓				✓
Centre for Eye Research Australia (CERA)[41]	✓			✓	✓
Hunter Medical Research Institute Research Register (Australia)[42]	✓				✓
Torch Recruit[43]	✓	✓	✓		✓
OPYL AI/Opin (Australian)[44]	✓	✓	✓	✓	✓
ClinTrial Refer (Australian)[45]	✓		✓		✓
Antidote (US & UK)[46]	✓				✓
Trial Facts (International)[47]	✓			✓	✓ (international)
EVRIMA Technologies (Australian)[48]		✓			✓
TriNetX[49]		✓		✓	✓ (US based)
Deep 6[50]		✓			x (US)
InSite Feasibility (Oncoshot, Singapore- empowered by AI enabled patient to trial matching technology, translates de-identified data into precise analytics to cancer trial sites for feasibility)[51]		✓			✓ (Singapore based)
Clinials (researcher platform that uses AI to turn complex study protocols into plain language for patients)[52]		✓	✓		✓
CogStack (data extraction framework)[53]		✓	✓		✓ (UK based)
REDCap[54]				✓	✓ (US based)

Qualtrics (platform being used for patient consent and data collection)[55]				✓	✓
State initiatives digitization of electronic medical records (Australia – QLD[56] and in NSW[57])		✓	✓	✓	✓
EpicEMR[58]		✓	✓	✓	✓
ICON**[59]				✓	✓ (International)
Medpace**[60]				✓	✓ (International)
CMAX Clinical Research[61]	✓				✓
CSL Limited[62]	✓				✓ (US based)
Nucleus Network[63]	✓				✓ (and US)
GenesisCare[64]	✓				✓ (UK, Spain, US)
ePROMS[65]				✓	✓
Health Research (A nativve service)[66]		✓			✓ (UK based)
Australian Healthcare Solutions[67]				✓	✓

*Definitions of categories: 1) Registers: patient-matching databases, clinicians looking for trials, patients looking for trials; as long as trial information is available and participants can find contact information to enrol in a suitable trial pending eligibility checks, 2) Artificial intelligence (AI): technologies that utilise artificial evidence to support participant recruitment, including machine learning and natural language processing, 3) Platform/Framework: requirement for infrastructure integration that utilises data for recruitment, 4) Other: Includes in-house technologies/platforms and data collection tools.
** Company specific technology

Additionally, recruitment into clinical trials could occur via the following methods:

1) Clinical Quality Registries (CQRs) (Australia and International)[29,68,69]
2) Research registries initiated by patients[70]
3) Teletrial Model as an avenue for improving recruitment of those living in rural and regional and remote communities[71]
4) National One Stop Shop – national approach specific to Australia[31]

Emerging opportunities and potential solutions

Emerging opportunities include recruitment into trials from primary care, a sector with huge potential as this would engage with underrepresented populations who are often excluded from research initiatives. This potential impact of including pharmacist intervention as part of engaging with primary care in clinical trial enrolment has been explored in the international clinical trial space, primarily in the United States[17] and offers potential benefits for enhancing patient recruitment in the Australian clinical trial sector.

Furthermore, Australia has an international presence in developing high standards of clinical quality registries (CQRs), and one key approach to harness the utility of CQRs would be to use technology to better integrate clinical trials with CQRs to enhance patient recruitment into trials.

When considering future enrolment into clinical trials, proposed solutions should be based on existing research into the sector and discussion on emerging capabilities (subject to a feasibility study), in particular:

- Digitisation of data to facilitate cross jurisdictional data sharing and solution for national recruitment
- Use of technologies to integrate clinical trials with clinical quality registries to increase the quality of targeted recruitment and patient retention into clinical trials
- Utilising technology to enhance recruitment into trials from primary care, including utilising pharmacies for recruitment

Some of the proposed solutions include:

1) Optimisation of selected existing platform(s) for wider coverage and enhanced uptake nationally
2) Financial resources into a national effort of:
    - Digitisation of medical data to facilitate cross jurisdictional data sharing (modelling after the UK initiative)
    - Enhancing the utility of CQRs to improve recruitment into clinical trials
    - Utilising technology to enhance recruitment into trials from primary care
    - Dedicated funding stream for clinical research support staff (upskilling research workforce, lack of site research support staff is a barrier to recruitment, perhaps shared funding models where support staff salaries can be subsidised by state or federal grants, or a levy onsite payment is something to investigate)
3) Waiting for the National Front Door initiative (subject to funding and time constraints)

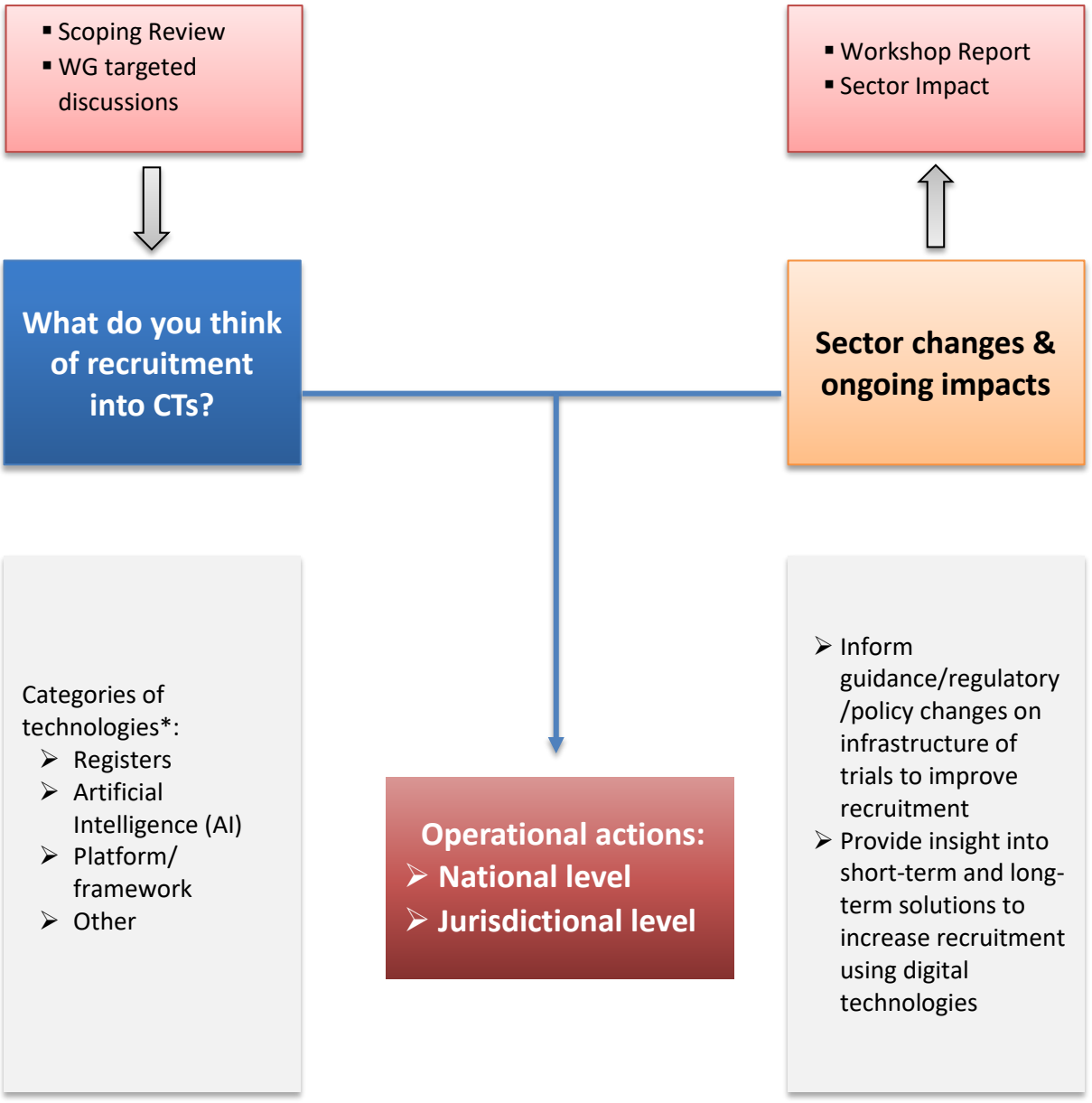
ACTA's activity outcomes

The outcomes for this activity are as follows:

Short-term outcome: Greater awareness of new recruitment technologies
Medium-term outcome: Increased efficiency of recruitment
Long-term outcomes: Faster recruitment into clinical trials; Increased visibility of clinical trials available in Australia

ACTA will hope to achieve these outcomes through showcasing case studies with emerging clinical trials within ACTA's member networks where successful recruitment had been achieved using technology. Faster and a broader representation of recruitment into clinical trials is a key objective of multiple stakeholders, including state governments and industry. We acknowledge the significant contributions by these other parties, and in the coming months ACTA will identify ways to meet this activity's outcomes by engaging with the various experts in our working group committee.

A summary of the process we hope to achieve with this project deliverables is outlined below:



*Definitions of categories: 1) Registers: patient-matching databases, clinicians looking for trials, patients looking for trials; as long as trial information is available and participants can find contact information to enrol in a suitable trial pending eligibility checks, 2) Artificial intelligence (AI): technologies that utilise artificial evidence to support participant recruitment, including machine learning and natural language processing, 3) Platform/Framework: requirement for infrastructure integration that utilises data for recruitment, 4) Other: Includes in-house technologies/platforms and data collection tools

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