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Trial and error

Supporting age diversity in clinical trials

Health and care
Community
Prevention
International
Inequalities
Life expectancy
Economy
Diseases and Conditions

Acknowledgements

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Executive summary

In an ageing world, more and more of us will be using medications later in life. However, despite the majority of medicine users being aged 60 and over, many trials still exclude older people.

This risks people taking medications that may not be as effective for them as they could be, or even worse, that lead to adverse reactions. Most clinical trial stakeholders agree that drug trials should include all groups who will find them useful. However, there are a number of barriers to conducting age-diverse trials:

Cost

- Involving older participants can require more resource and flexibility from trial teams. It's often considered easier and cheaper to use younger, healthier cohorts, as they are understood to carry a lower risk of adverse events. This is an assumption about older patients that requires further interrogation.

'Clean' data

- Recruiting younger cohorts often results in 'cleaner', less complex data sets. This can make any conclusions drawn about the efficacy of the medicine less accurate and less generalisable to larger populations.
- Removing older participants tends to remove some of the necessary complexity, including comorbidities and concomitant medications.
- Although 'clean' data may sound preferable, it reduces the nuance and diversity necessary in a trial and doesn't help researchers to understand whether medicines are safe and effective for all patients who may take them.

Arbitrary exclusions

- Some trial protocols allow individuals to be excluded from participation due to other diagnoses or concerns about compliance. Protocols may exclude certain groups (such as older people) disproportionately and without good reason.

Practical considerations

- The burden of treatment, and access difficulties, may form practical barriers for many older people.

Three decades ago, in 1993, pharmaceutical regulators came together with the industry to identify wide-ranging concerns about the lack of age diversity in clinical trials and then made recommendations to improve this.

Over recent decades we have seen an increase in initiatives to improve inclusion of underrepresented groups, particularly with regards to gender and race. However, we have not seen enough progress on age diversity to match this. Recent developments in remote and flexible trial designs have made participation more accessible than ever. Yet action is required across the board to ensure that older patients are able to leverage this increased accessibility. We need structural and cultural change to ensure that the people who use medications and treatments are adequately represented in the trial process.

Recommendations

All stakeholders

- Co-production of new guidelines to update and replace the existing International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH-E7) guidelines, which specify requirements for facilitating age diversity in trial cohorts. The ICH-E7 guidelines were published in 1993 to support age diversity in trials, but this report finds that they do not go far enough. Regulators could collaborate with pharmaceutical companies and other stakeholders to co-produce new guidelines
- A gold standard for inclusive trials would make it easier to identify best practice

Regulators

- Regulators to galvanise action on age diversity, and incentivise increased investment in diverse trial cohorts across the industry

Researchers and pharmaceutical companies

- Pharmaceutical organisations to appoint diversity champions to prioritise age diversity
- Pharmaceutical organisations to continue to prioritise technological advances for the benefit of older populations
- Funders and institutions to ringfence resources to develop consistent PPI infrastructure
- All researchers and pharmaceutical organisations to prioritise gathering age-related data throughout all trials
- Diversity and inclusion (D&I) initiatives to be expanded to prioritise age diversity

About this report

This report draws on a review of the existing literature, as well as findings from a roundtable of experts hosted by ILC in January 2023 and subsequent one-to-one interviews with eleven expert stakeholders.

The roundtable and interviews included:

- Pharmaceutical professionals
- Regulators
- Academic researchers and clinicians from pharmacology, geriatrics, public health and sociology
- Contract research organisations
- Patient advocacy professionals
- Healthcare technology professionals
- Other associated professionals

These were conducted under Chatham House Rules.

The scope of this report doesn't cover specific issues involved with clinical trials that involve children. However, additional research into the effects of medicines on children is also clearly required.

The aim of this report is a broad overview of the opportunities and challenges of age diversity across healthcare systems. All recommendations will look different within the context of a specific nation's regulatory framework. Specific regulations and standards vary from one jurisdiction and country to another. National governments, as well as supranational institutions like the EU, should put in place legislation, regulations and recommendations adjusted to match their own situation.

What's the problem?

Most drugs are used by people aged over 60, yet trial participants are often younger.

Patients receiving medications in hospital and in the community tend to be older than the general population. A global review of the literature on this topic finds that on average, between 2 and 9 medications are taken every day by people aged 60 and over across different countries and populations.[1] This trend has also been observed across the other nations of the UK, and internationally.

This means that there are several reasons why age should be a key consideration when evaluating the diversity of a trial cohort:

- Metabolic clearance[a] varies significantly between age groups, so the effect each medicine has is likely to vary for patients of different ages.
- Immune response declines naturally with age, so older patients will have different health needs: there's a specific range of medicines and interventions developed to accommodate this.
- Other changes, including cardiovascular and pulmonary issues, can cause a higher incidence of certain diseases among older people. This greater incidence of certain diseases means that older patients need specific medicinal interventions that are not currently being developed.

We know that older people are more likely to be taking multiple medications. This is particularly the case in care homes; concerns have been raised that adverse events could be caused or increased by polypharmacy (simultaneous use of multiple medicines) and poor medication management.[2]

Care home residents are prescribed an average of seven medications a day, with many taking more than ten drugs daily.[3] In the USA, overprescribing of common medications is particularly prevalent among older patients.[4] Management of, and patient adherence to, prescribed medications is an ongoing problem that was highlighted in 2017 by a World Health Organization Global Patient Safety Challenge, *Medication Without Harm*.[5]

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[a]Metabolic clearance is the time it takes a person to digest the medication into their bloodstream.

Although younger cohorts can sometimes be appropriate, depending on the stage of the trial and the type of medication, problems arise when trials of medications intended for older people don't include enough older people. Such trials don't generate sufficient evidence that the medication is safe and effective for older populations.

Furthermore, trying to predict an individual's health based on their age group is difficult and doesn't often produce helpful conclusions. When we spoke to them during our research for this report, clinicians and trial design experts frequently cited increasing variation in health between different patient groups of the same age. This affects how symptoms are experienced, and the burden of the trial on everyone. Older trial participants exhibit the compounding effects of their individual lifestyles and health behaviours over several decades. This means people of similar ages, possibly with the same condition, will arrive at the trial with completely different health concerns and experiences of the healthcare system thus far. Two people of a similar age could therefore have a completely different experience of the trial itself.

> ***"If ageing does anything, it makes us more diverse, not less."***
>
> **Roundtable attendee: academic researcher into the biology of healthy ageing**

It's important that trials capture this diversity as much as possible, for the benefit of the patients who will be prescribed the medication later. For example, plenty of older people could be taking medicines that won't improve their health outcomes. Continuing to prescribe ineffective medicines is expensive; we believe that it's an unnecessary drain on the resources of already-overstretched healthcare systems. Age diversity is crucial to securing the evidence that older patients deserve, and supporting clinicians to prescribe medicines that are effective and provide value for money.

What standards are currently in place?

Three decades ago, pharmaceutical regulators worked with the industry to identify wide-ranging concerns about the lack of age diversity in clinical trials; the regulators made recommendations to improve this.

In 1993, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) published a set of guidelines referred to as ICH-E7. This was intended to assist those designing, delivering, and funding trials in making them more age diverse. It included the following guidelines:

- Drugs should be studied in all age groups for which they will have significant utility
- Patients entering clinical trials should be reasonably representative of the population that will be later treated by the drug
- It is important not to unnecessarily exclude patients with concomitant illnesses

These guidelines were taken up and supplemented with non-binding recommendations,[6] including:

- Inclusion of at least 100 older participants at phases 2 and 3 to allow for the detection of clinically important differences (a study in 2020[7] found that recent trial designs broadly failed to meet this target)
- In the applications to regulators for approval (called marketing applications), participant data should be presented by age group, to give doctors and patients a clear understanding of who was involved in the trial when deciding whether to use that drug
- Where a trial hasn't been able to enrol enough older patients (despite the best efforts of the trial team), a specific plan to collect post-marketing data should be drawn up and submitted with the marketing application

As industry colleagues are aware, once a trial is completed the medication must be licenced by a regulatory body (the Medicines and Healthcare products Regulatory Agency in the UK; the Food and Drugs Administration (FDA) in the US) and recommended for use in clinical settings. Each healthcare system has a body (NICE in the UK) that appraises the medicine, weighing up its cost against the likely benefits for those it's designed to help. Marketing applications are evidently a

touchpoint where medicines are evaluated for their suitability for different age groups, and an opportunity to ensure age-diverse cohorts to support age group recommendations.

Even if a medicine ticks all these boxes, it has not yet completed its journey. Clinicians must have confidence in the medication and its supporting evidence before they will prescribe it to the patient sitting in front of them.

What are the barriers to achieving age diversity?

In this section, we consider the needs and experiences of three main stakeholder groups, as well as common areas where barriers to achieving sufficient age diversity in clinical trials may be found.

By stakeholder

Participants

A 2012 UK study known as the PREDICT study[8] asked patients and carers to set out why, from their own perspective, older participants might be disproportionately excluded from clinical trials. Four themes were most frequently cited:

- Ageism in society and the clinical/research environment
- Older patients more clearly understood the disadvantages and risks of participation, which they perceived to outweigh the possible advantages
- The patient's relationship with the clinical team (most importantly with the physician who invites them to participate)
- The practical aspects of participation, including transport and the accessibility of trial centres and locations

While these aren't the only barriers to diverse trial cohorts, they're recurring themes cited by patients and patient interest groups.

Each participant's journey through a trial is unique, from being unaware of the trial, through recruitment and participation, and finally completion. Clinical trial research teams, in this country and overseas, have access to patient and public involvement (PPI) groups and infrastructures to provide insight on participants' perspectives and help ensure that trials are designed around their needs. PPI is an umbrella term that can include public consultations, patient engagement initiatives, and research co-design.

PPI groups have a formal role, which is providing consultation to researchers to ensure that their decision making is inclusive and accounts for first-hand experience of the relevant condition, treatment and healthcare system. But informally, members of PPI groups may also be proactive in patient support and advocacy networks, or work with charities relating to that condition. They may spread information about trials and offer peer-to-peer support for participants. Unfortunately, not

all research teams engage with PPI groups to the same extent; particularly if they lack support to find or create their own PPI networks for each new trial.

During the roundtables and interviews conducted for this report, our experts emphasised the importance of trust between a potential participant and the clinician who invites them to take part in a trial. This single interaction can determine the participant's understanding of the trial, their decision to participate, and the likelihood that they remain in the trial until the end.

This means that recruitment discussions with potential participants carry a lot of weight. Several experts we spoke to in our research indicated that clinicians must continue to meet their patients where they are and ensure that participants understand the trial process throughout. This helps participants stay motivated to remain involved and manage any changes to their health, whether those result from the trial or any pre-existing conditions. For this, clinicians need a good understanding of each individual's medical history, key concerns, and motivation for joining the trial.

Researchers

If researchers were to provide tools for recruiting more older people in clinical trials, pharmaceutical companies and other stakeholders would have more confidence to take risks (or what they perceive to be risks). This means creating the necessary resources to support the recruitment of participants with more complex needs and medical histories.

Although patient-centred care and evaluation is necessary for clinical trials, it could be possible to categorise and quantify ranges of symptoms and/or conditions. This wouldn't be straightforward – for example, researchers have not yet reached any consensus as to what constitutes "frailty" and what the indicators of "frailty" would be. So creating a taxonomy to describe frail or unwell patients could have some utility; it would help to define parameters as to how healthy someone must be to be recruited. Researchers could use these participant categories in guidelines and design parameters, and to help determine trial recruitment criteria.

Traditionally, one first point of contact for recruitment is a healthcare service treating the specific diagnosis relevant to the trial. Another is through targeted efforts to contact patients with a specific condition.

But it could be more efficient to create an online database of people (such

as Our Future Health, which is currently being rolled out in England)[9] who have volunteered to participate. Researchers could search the database for specific criteria, such as age, and contact the relevant volunteers for recruitment into specific trials. This approach could become the norm as remote and digital trials begin to remove geographic limitations.

Pharmaceutical companies

Identifying, recruiting and catering for more diverse cohorts of trial participants is expensive, as is dealing with the more complex data sets that result from that diversity. The organisations and institutions that organise clinical trials have a clear commercial incentive to keep trial costs as low as possible.

Recruiting older participants can require more resource and flexibility from trial teams. It's often easier and cheaper to use younger, healthier cohorts, as they tend to carry a lower risk of adverse events.

However, this should be balanced against the commercial benefit of undertaking rigorous trials that show the medications being studied are demonstrably safe and effective for more people, including those with comorbidities and concomitant medications. In a world where the population is ageing and the market for such medications is increasing, it can be worthwhile to make the increased investment of money, time and resources required.

Trial design

When designing a trial, trial protocols provide the roadmap for recruitment and how the trial is conducted.

Our roundtable attendees emphasised that the principal investigators (PIs) and chief investigators (CIs) who design these protocols must prioritise age inclusivity within trial design and recruitment decisions. When considering diversity, they must ensure that age is considered on a par with disability, gender, and ethnicity moving forward.

> ***"You can't deliver a trial in an inclusive way if it hasn't been designed in an inclusive way."***
>
> **Roundtable attendee: geriatrician**

Trying to capture a moving target

Large cohorts such as the 'over-50s' and 'over-65s' are by their natures very diverse, with increasingly varied and complex needs. Our ageing

and growing population also means that for every drug under study, the proportion and absolute number of older users will continue to grow. Larger populations also mean more diversity and complexity.

Our roundtable experts raised the idea of a target for older participants being a 'moving target' several times during our conversations. This refers both to the inability to pin down exactly who we mean by 'older' participants, and the difficulties of capturing real-world diversity in trial cohorts.

A preference for 'clean' data

Trial design often favours younger, healthy participants because this delivers cleaner data, unmarred by comorbidities and high rates of non-completion. In some trials it will be necessary to initially limit participants to healthier, younger cohorts in order to demonstrate the safety of the drug.

But after this initial stage, it would be appropriate to include older groups of participants and those with more complex health needs. Every trial should prioritise efficacy and safety in older cohorts, particularly in medicines for conditions that list age as a risk factor. Older participants and those with complex needs, including comorbidities and concomitant medications. are likely to bring additional data points and less likely to remain in a trial until the end. This must be accounted for when studying trial results if researchers are to understand the effect of the medicine or intervention.

Concomitant medications are those taken by a trial participant in addition to the drug being studied by the trial. They are a significant challenge to trial designers, as combining medications brings an increased risk of adverse events and makes drawing conclusions about the trialled drug's efficacy more difficult. It may be possible to avoid this problem by using "digital twins"[10] (also known as digital patients or virtual patients) alongside real-world trials. These are computational models generated from a range of different types of patient data, population data, and real-time updates of different variables. This involves generating an analysis of the molecular processes that will take place when the drug is metabolised.

Using digital twins, clinicians may be able to make some predictions about how patients might respond to the drug, or a combination of drugs. Although these programmes are in the early stages of development, collaboration between health services and the private companies developing digital twin technology would support effective

and targeted development that generate more information about trial safety. Eventually this technology could be rolled out to complement the participation of physical patients.

Our expert stakeholders suggested this type of public-private partnership as a good solution. Combining the existing infrastructure, reach and expertise of the public sector with the innovation, flexibility and investment of the private sector could achieve more effective and far-reaching results than any organisations working independently. Our experts pointed to the swift development of COVID-19 vaccines to illustrate what's possible when private and public organisations collaborate to achieve a common objective.

Case study

RECOVERY is a UK-based international clinical trial that identified treatments for people hospitalised with suspected or confirmed Covid-19.[11] It has been credited with changing the landscape of clinical trials and democratising trial participation. It's unsurprising that such breakthroughs were made to find treatments during a global pandemic, but the novel uses for routine data in this trial made it particularly effective. Patient involvement and all other trial procedures were streamlined using digital platforms that required minimal manual data entry and automatic randomisation of patients.

Exclusion criteria

While arbitrary upper age limits are no longer generally acceptable in trial protocols, there may still be exclusion criteria that indirectly and disproportionately exclude older participants. This includes ruling out individuals with specific diagnoses, sometimes without reference to the degree or severity of that condition. One 2021 study from the USA found that hypertension, diabetes, anaemia, all of which are more common conditions in older people, and "any condition the study investigator considers ineligible for clinical trials"[12] could preclude participation.

Blanket exclusion on the basis of certain diagnoses may be clinically necessary in some trials. The benefits of each trial must be balanced against the burden it places on participants. However, these decisions must be justified at each stage of the trial design and delivery, to determine which exclusions are necessary and which aren't. This requirement could be reinforced through accountability to existing regulatory structures and patient and public involvement (PPI).

The same US 2021 study[13] of trial protocols revealed that non-specific and unjustified "concerns around compliance" could act as a barrier to older people's participation in trials. In this instance, trial researchers may exclude certain individuals at their own discretion, due to lack of specificity in some protocols.

In addition to compliance concerns, clinicians might be cautious of recruiting participants if they think that health status or other factors may prevent them from completing the trial. Age could play a key (and disproportionate) role in their decision as to whether an individual should be recruited.

This is where the ageism reported in the PREDICT study[14] might surface. This is a study conducted in the UK 2012, asking older patients and carers about their experiences participating in clinical trials. One of the key themes that emerged was the extent to which ageism in society and in the clinical/research environment affected older participants' experiences of trials. Ageism could present in different ways, including arbitrary upper age limits, or a failure to justify why some older participants were excluded, if not on the basis of age. Older patients who actively sought to participate in trials reported facing unnecessary barriers relating to their age.

Trial delivery

The Covid-19 pandemic has had an impact on trial delivery by advancing decentralised clinical research models. Moving away from the traditional model of trials based in hospitals and research centres can help to overcome some of the practical difficulties faced by older participants. During the pandemic, alternative methods, such as: phone consultations; virtual, decentralised or siteless trials; and digital tools for patients to report outcomes (electronic patient reported outcomes or ePROMs) proved essential for keeping trials on track while complying with social distancing requirements.

Many trial designs continue to implement more flexible ways of working, which support more diverse trial cohorts.

Exploring new ways of working that are sustainable and effective in the longer term is a crucial step towards supporting more diverse clinical trial cohorts. Participants are more likely to commit to a trial with a welcoming environment, where they feel accepted as they are.

> ***"Most successful trials are designed from a lived-experience perspective that is culturally centred."***
>
> **Roundtable attendee: patient engagement expert**

Some trials may recruit more older patients with complex needs than others, depending upon the condition or diagnosis the intervention seeks to address. This is because one factor that can help researchers predict whether an individual will complete their trial is the nature of their relationship with the condition the medication seeks to treat, and consequently with the clinical team. Our roundtable and interview experts indicated that trust in the clinical team tends to be built through sustained contact, often during treatment of chronic and long-term conditions. By contrast, more short-term interventions such as vaccines may not come with an established level of trust in the clinician delivering the intervention.

Clinical trial teams can build trust and mutual understanding with participants through interactions and mutual discussion. This is often facilitated through PPI groups who draw on their own experience of their conditions (and any experiences of participating in research), to help researchers prioritise what they will research, and create inclusive trial designs. These resources give older people the chance to share their opinion on what works, and what should be a research priority.

Clinical trial institutions are increasingly working with PPI groups to support diverse, inclusive trials and studies. This is the most effective way to ensure trial objectives are in line with patient need, and trials are accessible to a range of participants.

But one of our experts highlighted the challenges of developing this infrastructure:

> ***"It's often left to research teams to form their own PPI structures. Universities are autonomous and have different funding pots and have their own constitutions and policies, which influence the type of PPI involvement they might be able to create."***
>
> **One-to-one interviewee: health sciences researcher**

It would be beneficial for universities to ringfence funding within each science/ research department, allocated specifically to PPI infrastructure.

Trial funding

Clinical trials are expensive endeavours, and trial organisers routinely procure funding from different sources.

One strategy for promoting inclusion is making funding conditional upon diverse cohorts. However, during our roundtable, our experts indicated that trial organisers can follow the letter of such regulations without engaging with the spirit. In a hypothetical example, a trial might be required to include a certain proportion of participants aged over 65. In this case, the trial organiser might recruit the stipulated number, but with most of the participants aged between 65 and 70. This would meet the stipulated criteria and achieve a certain degree of age diversity. However, it would supply minimal data on how this medicine would affect people aged 70 and over.

We must strike a balance between making age-inclusive targets ambitious and keeping them realistic, to avoid a burden that's detrimental to the trial's primary objectives. Open dialogue between organisers, PPI groups and regulators can help to identify opportunities for improvement and collaboration to support more diverse trial recruitment.

Regulators

Regulators are already working to strike a balance between supporting innovation and enforcing the rules and restrictions that ensure safety. As already mentioned, from the industry perspective there's a clear commercial imperative to exclude older participants and prioritise younger healthy people – it's cheaper to conduct trials this way.

Regulators must therefore create incentives to prioritise inclusivity in trial design and delivery. Funders must be supported in planning for the added complexities and costs attached to diverse cohorts. It makes sense for funders to be risk-averse: more information and support from regulators could help funders and trial researchers to take more calculated risks.

One stakeholder suggested that regulators could have better conversations with pharmaceutical companies and researchers, about how to evaluate the results of trial and be firmer about requiring results to be truly applicable and useful:

> ***"The European Medicines Agency needs to be more assertive in refusing data packages if [they don't] adequately demonstrate patient benefit."***
>
> **One-to-one interviewee: medical science expert**

Regulators could also use their position to advocate setting trial costs against future gains to pharmaceutical companies. Pharmaceutical

businesses are often risk averse; framing the discussion around quality assurance and the perceived quality of trial data by clinicians could address concerns about the increased costs of recruiting older participants. Ensuring that a new drug's trial has a suitably diverse cohort will generate more transferable and reliable evidence, leading to improved clinical confidence in the drug.

Making trial information accessible to potential participants is a key step towards building trust and confidence in the trial and clinical team. The past few years have brought a new focus on inclusive and culturally appropriate communication and relationship-building within the clinical trials space. The COVID-19 pandemic also highlighted the importance of a base level of societal scientific literacy, which helps to build trust in science and medicine. A key aspect of this in trials is swiftly and clearly communicating results and outcomes to participants. Individuals want to understand the impact of their contribution; making concerted efforts to communicate this builds trust between clinicians and PPI groups.

Accessible information is crucial to adherence and patient confidence when taking their medications. One expert stakeholder advocated for simple one-page summaries, both included in the medication box or packet and accessible through a QR code. These should answer the most common Q&As, for instance:

- What should I do if I miss a dose?
- Can this tablet be crushed and consumed in food?
- What are the most common side-effects?

As well as allowing more patients to have more understanding and control over their medication, such measures could improve adherence. This resource would be particularly valuable for paid carers; they are tasked with administering medication but may not have sufficient background knowledge about the patient and their medication to do so with confidence.

Case study

As of February 2023, the US has a statutory requirement that applications for late-stage approval of clinical trials submitted to the FDA must include diversity action plans. The plans must describe the funder's/researcher's goals for increasing enrolment from underrepresented groups and explain how these goals will be achieved. The primary focus is currently on racial and ethnic diversity,

which is sorely needed to address the long-standing inequality of access and care for non-white patients.

However, the FDA draft guidance from April 2022[15] mentions age several times, and the document refers to the FDA's guidance on inclusion of older people. The most recent guidance refers specifically to including older participants in trials for cancer treatment.[16] Although many of the recommendations for cancer trials will be transferable to other areas of medicine, further work is required to support the participation of older patients across the board.

Recommendations

These recommendations are the result of the roundtable discussion and following discussions with a further eleven experts. The findings and varied experiences of the range of experts we spoke to have been collated here; many of these recommendations are actionable by stakeholders at all stages of the trial process.

Regulators to co-produce new guidelines to update and replace ICH-E7, which clearly specify requirements for facilitating age diversity in trial cohorts

- Vast technological developments and cultural shifts have taken place in the past three decades. The ICH-E7 and accompanying Q&As from 1993 don't address current trial diversity challenges.
- New guidelines will need input from all stakeholders, particularly from older people, gerontologists, and regulators.
- Every trial is unique; it wouldn't be workable to specify set numbers or percentages of older participants. Stakeholders can work together to determine acceptable standards, taking the real-world factors that adversely affect recruitment into consideration.
- Guidance would set out actions and targets that are ambitious without being overly burdensome.

Regulators to incentivise increased investment in trial cohort age diversity

- PPI infrastructure, flexible trial designs, and inclusive practices are expensive. Trial funders currently have a commercial imperative to conduct trials in a way that reduces costs while producing acceptable results. Regulators and industries must reward meaningful cohort diversity, while simultaneously creating policies and regulations that require action towards improved diversity.
- Age is a risk factor for a variety of conditions; there will soon be more older patients, requiring more medical interventions, than ever before. Regulators can emphasise that it's in the best commercial interests of funders and pharmaceutical organisations to demonstrate that their products are effective for older patients, as these markets continue to increase.
    - Catering to the world's ageing populations also provides an opportunity for institutions and projects to demonstrate that

they can take the lead in the anticipation of, and response to, demographic change.

Pharmaceutical organisations to prioritise gathering age-related data throughout all trials

- Diversity champions (see below) could gather data to build a more comprehensive picture of what works for different groups of older people. This would also build confidence among clinicians and patients that any recommendations relating to medications for older people are based on sufficient data.
- This data would substantiate the other recommendations made in this report; we cannot improve age diversity without a clear understanding of how we are currently doing on this issue.
- An obligation to gather and evaluate this data would ensure that age diversity is high on the agenda.

Researchers to expand diversity and inclusion (D&I) initiatives to include age and other characteristics

- Focusing on specific characteristics in isolation isn't enough. Researchers must consider the intersection of all the characteristics that are medically and socially relevant to trial outcomes.
- In addition to ethnicity and race, this includes, but isn't limited to: age, socioeconomic status, disability, gender identity and sexual orientation.
- Legislators and regulators should expect, and have appropriate powers to require, that all other actors take action on D&I beyond what's currently in place.

Regulators to create a gold standard for inclusive trials

- Regulators and pharmaceutical companies should work together to devise a method of classifying the trials that prioritise age diversity in their design, recruitment, and delivery, to earn the trust of prescribing clinicians and patients.
- Only the trials that go above and beyond to incorporate intersectionality into their diversity and inclusion strategies would be eligible for such a commendation.

Pharmaceutical organisations to appoint diversity champions to prioritise anti-ageism

- Each organisation should appoint or recruit a named Diversity Champion. Where they already have them, organisations should ensure that their responsibilities include championing age as an important characteristic.
- Diversity champions should facilitate trial researchers undertaking meaningful engagement with trial participants and the wider public.
    - This could include focus groups, networks/links with underserved community groups, or engagement with other patient interest groups.
- Diversity champions should also advocate post-marketing data collection in cases where insufficient numbers of older people were included in the trial.
- The PI & CI for each trial should collaborate with their organisation's Diversity Champion to effectively explain the results of the trial and disseminate that information to participants, interested communities and PPI groups.

Pharmaceutical organisations to invest in technological advances for the benefit of older populations

- Continuing to develop "digital twin" computational models, with wider subsequent adoption, could provide a valuable resource for testing alongside physical trials. This could also mean some trials wouldn't need to recruit "physical twin" participants until later stages.
- Other technologies that are currently in use, including remote and decentralised trial designs, should be re-evaluated frequently to ensure that their use is inclusive and supports the participation of a diverse range of people.

Funders and institutions to ringfence resources to develop consistent PPI infrastructure

- People participate in trials because they want to contribute to effective research and to the development of medicines that will help people. They tend to complete trials more often when researchers have established a trusting relationship with them. Creating permanent networks of patients, carers, and other community members could facilitate trial recruitment and communication, if trial

researchers consult these networks at every stage to ensure that their trials are accessible and workable for older participants. It would use fewer resources than creating such a network from scratch for each trial.

- Many patients who complete trials don't fully understand the results, where their information has gone, and what happens next. PPI networks can allow communication via different channels and help participants to share information and discuss their experiences with each other. Older participants with complex needs may stay in trials for longer if they have social connections with people going through the same trial.
- Trial organisers should co-produce agendas and trial strategies with PPI groups at every possible stage. As well as increasing trust and participation, this can help to identify potential issues and barriers in trials before they arise, with benefits in terms of trial quality and sustained involvement.

Conclusion

To achieve meaningful age diversity in clinical trial cohorts, stakeholders involved at any stage of the process must go over and above what is currently required.

This includes thorough and consistent patient involvement, more investment of time and resources into PPI networks and infrastructure, and regulatory changes to support dialogue between regulators, pharmaceutical companies, and trial designers. Regulatory requirements must include diversity action plans that include all relevant protected characteristics and broaden the focus of existing D&I strategies to be more intersectional.

Centring the needs and experiences of older people throughout is vital if we are to improve recruitment and completion rates. It will also mean a better end product which is more suited to changing global demographics. Clinical trials are complex, expensive, and necessary for the good health of populations who are simultaneously increasing and ageing.

The potential benefits for population health and trust in the healthcare and pharmaceutical industries are significant and commercially worthwhile.

This report makes the case that we should all go the extra mile to include people of all ages with the understanding that this is an investment in our future collective health.

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[12]https://pubmed.ncbi.nlm.nih.gov/32986099/

[13]Ibid

[14]https://www.openaccessjournals.com/articles/the-views-of-older-people-and-carers-on-participation-in-clinical-trials-the-predict-study.pdf

[15]https://www.fda.gov/media/157635/download

[16]https://www.fda.gov/media/156616/download

About ILC

The International Longevity Centre UK (ILC) is the UK's specialist think tank on the impact of longevity on society. The ILC was established in 1997, as one of the founder members of the International Longevity Centre Global Alliance, an international network on longevity. We have unrivalled expertise in demographic change, ageing and longevity. We use this expertise to highlight the impact of ageing on society, working with experts, policy makers and practitioners to provoke conversations and pioneer solutions for a society where everyone can thrive, regardless of age.

International Longevity Centre UK

Vintage House
36-37 Albert Embankment
London SE1 7TL
Tel : +44 (0) 203 242 0530
www.ilcuk.org.uk