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NEW HORIZONS

New horizons in evidence-based care for older people: individual participant data meta-analysis

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Abstract

Evidence-based decisions on clinical and cost-effectiveness of interventions are ideally informed by meta-analyses of intervention trial data. However, when undertaken, such meta-analyses in ageing research have typically been conducted using standard methods whereby summary (aggregate) data are extracted from published trial reports. Although meta-analysis of aggregate data can provide useful insights into the average effect of interventions within a selected trial population, it has limitations regarding robust conclusions on which subgroups of people stand to gain the greatest benefit from an intervention or are at risk of experiencing harm. Future evidence synthesis using individual participant data from ageing research trials for meta-analysis could transform understanding of the effectiveness of interventions for older people, supporting evidence-based and sustainable commissioning. A major advantage of individual participant data meta-analysis (IPDMA) is that it enables examination of characteristics that predict treatment effects, such as frailty, disability, cognitive impairment, ethnicity, gender and other wider determinants of health. Key challenges of IPDMA relate to the complexity and resources needed for obtaining, managing and preparing datasets, requiring a meticulous approach involving experienced researchers, frequently with expertise in designing and analysing clinical trials. In anticipation of future IPDMA work in ageing research, we are establishing an international Ageing Research Trialists collaborative, to bring together trialists with a common focus on transforming care for older people as a shared ambition across nations.

Keywords: ageing, frailty, stratified care, individual participant data, meta-analysis, older people

Key Points

- Evidence-based care for older people is best informed by meta-analysis of intervention trial data.
- To date, meta-analyses in ageing research have typically used summary (aggregate) estimates from published trial data.
- This has limitations regarding which subgroups of people stand to gain most benefit from an intervention, or are at risk of harm.
- Individual participant data meta-analysis (IPDMA) uses the original trial data, enabling examination of individual characteristics that predict treatment effects.
- IPDMA could transform care for older people through stratified care—targeting interventions to those most likely to benefit.

Introduction

In this New Horizons paper, we outline the limitations of standard meta-analysis methods that synthesise evidence using aggregate data from ageing research intervention trials. We describe how future evidence synthesis using individual participant data from trials for meta-analysis could transform understanding of the effectiveness of interventions for older people, supporting evidence-based and sustainable commissioning. We place a particular emphasis on identifying and testing predictors of treatment effects, to support matching of older people with specific treatments based on their individual characteristics such as frailty, disability, cognitive impairment, ethnicity, gender and other wider determinants of health as the basis for stratified care. The approach has relevance across an array of interventions for important age-related conditions and geriatric syndromes, including frailty, falls and dementia care spanning a range of settings including primary and community care, secondary care and care homes. Extension of the approach across related areas, for example cardiovascular risk management in older age, could support individualised treatment decisions that are based on robust prediction of response to a range of pharmacological and non-pharmacological treatments.

Context

Across the world, populations are ageing now more than ever, and maintaining the health and independence of this growing older population is a key consideration across all nations [1]. In recognition of this, the establishment of systems of care for older people based on robust evidence of clinical and cost-effectiveness of interventions is a stated global priority [1]. To maximise value from an individual and societal perspective, there is a growing consensus that interventions should be better targeted to those who are most likely to benefit [2].

Stratified care

'Stratified care' involves targeting treatments based on an individual's personal characteristics, typically by classifying individuals into subgroups that differ in their susceptibility to a particular outcome or their response to a particular treatment [2, 3]. It is recognised that a broad range of characteristics can be used to potentially stratify care, spanning biomarkers (measurable characteristics of biological processes—molecular, histological, radiological or physiological), clinical scores, comorbidities, medications, behavioural or psychological measures and demographic factors.

The term stratified care (or stratified medicine) has, over time, been used interchangeably with the terms precision medicine and personalised medicine [2, 4, 5]. Precision medicine has historically focused on use of biomarkers to better target pharmacological treatments, particularly for cancer and rare diseases [6]. 'Omics' technologies (e.g. genomics, proteomics, metabolomics), which involve a comprehensive assessment of a set of molecules, have typically been a core component of precision medicine. The concept of personalised medicine also arose from the explosion of data generated from genome sequencing but includes an explicit recognition of a requirement to have a broader view that takes into account wider characteristics to target treatment [4]. However, the term 'personalised medicine' means different things to different people, ranging from treatment based on an individual's cancer genome to the development of a personalised care plan, familiar to clinicians working in geriatric medicine and primary care. We use the term stratified care throughout this New Horizons paper for consistency, while acknowledging that whichever term is used the focus is ensuring that treatments, both pharmacological and non-pharmacological, are targeted to people who are most likely to gain benefit from them, and minimising risk of harm [2].

Evidence gaps

Clinical and health policy decisions on clinical and cost-effectiveness of interventions are ideally informed by meta-analyses of intervention trial data. However, when undertaken, such meta-analyses in ageing research have generally been conducted using standard methods whereby summary (aggregate) data are extracted from published trial reports. Although meta-analysis of aggregate data can provide useful insight into the average effect of interventions within a selected trial population, it has limitations regarding

robust conclusions on which subgroups of people stand to gain greatest benefit from an intervention or are at risk of experiencing harm. Examples of current evidence gaps include

- Whether comprehensive geriatric assessment (CGA) is more or less effective for older people depending on their level of frailty.
- Whether fall prevention interventions are equally effective for males and females, and whether effectiveness is related to baseline predicted risk of falling.
- Whether physical activity interventions for care home residents are equally effective for people with increasing levels of dependence.

Alongside these specific examples, there is a wider evidence gap on whether intervention effects differ based on important characteristics, for example ethnicity, sex or socioeconomic position.

Aggregate-level meta-analysis based on published data

The overall aim of a meta-analysis is to synthesise research evidence, for example from randomised controlled trials (RCTs) of interventions, thereby increasing statistical power and overall level of certainty in the intervention effect estimates. Standard meta-analytical methods rely on extraction of aggregate data from original trial reports, typically an effect estimate (e.g. risk ratio or mean difference) with related measure of distribution to enable synthesis in meta-analysis, for example standard deviation, *P* value or 95% confidence limits. Once extracted, summary estimates can be synthesised through meta-analysis to generate an overall estimate of intervention effect and quantify its uncertainty.

The main advantage of standard meta-analysis using aggregate trial data is that it is time efficient and with well-established and accessible methods. Key limitations of standard meta-analysis methods relevant for ageing research trials are that the meta-analysis is restricted to the outcomes and analyses that are reported in the individual papers. Trials may collect detailed information on characteristics of participants that could be useful as stratification factors but not report all information collected or not analyse the data as part of the main evaluation. Such information could include measures of mobility (e.g. gait speed, timed-up-and-go test), frailty (e.g. phenotype model, clinical frailty scale, frailty index (FI)), activities of daily living (ADL), grip strength, cognition and biomarker measures. It is also uncommon for individual trials to report on whether intervention effects vary by sociodemographic factors such as ethnicity, often because the number of participants from minority ethnic groups in individual trials is low. Considered collectively, this range of challenges means that it is difficult and often not possible to synthesise data on characteristics that are potentially useful to inform stratified care for older people using published data only.

A related problem is that using aggregate data for such individual-level variables (e.g. mean estimates or proportions extracted from trial reports) in a meta-analysis can lead to aggregation (ecological) bias. For example, there may be a strong relationship between cognition and intervention effect in individual trials, but if the mean cognitive score across trials is similar then no relationship will be apparent if the mean scores and aggregate-level effect estimates are combined across trials [7].

Furthermore, trialists may analyse and report outcomes using different methods that make the evidence problematic to synthesise using standard meta-analysis techniques. A common problem is that continuous outcomes may be reported as either change from baseline or final value scores at follow-up. Although there are methods to address this problem in aggregate-level meta-analysis, they involve multiple assumptions that may be problematic. For example, standard deviation estimates may be taken from other studies to derive change scores but this relies on whether the studies used the same measure, with the same degree of error, and at the same timepoints [8].

Individual participant data meta-analysis

IPDMA involves the collection, preparation, validation and analysis of the original individual-level trial data recorded for each participant [9]. Both aggregate-level and IPDMA are typically preceded by a systematic review of the literature to robustly identify the existing evidence in a particular area of interest. An IPDMA should be considered when aggregate data preclude a good quality review or are insufficient for detailed analysis [8]. Obtaining individual participant data (IPD) can support the addition of outcome data that were not reported in the published paper, or that were published but presented in a format unsuitable for meta-analysis. Preparation of the IPD can support standardisation of cut-points for measures, enabling additional analyses that may be precluded using aggregate data.

Crucially, IPDMA of intervention trials avoids aggregation bias and allows more flexibility in analytic approaches, addressing key limitations of aggregate-level meta-analysis. This includes detailed examination of characteristics that predict treatment effects—identifying subgroups that benefit most from an intervention or, equally, that do not benefit or are at increased risk of harm [9]. This can support development of stratified care based on targeting interventions for older people who stand to gain the most benefit from them, and avoidance of therapeutic nihilism based on individual judgements of which older people may not benefit from certain treatments.

Additional benefits of IPDMA can include improving generalisability of trial findings. This can be done by using population data to weight the IPD on the basis of the probability of participating in the trial, by using knowledge of characteristics that predict treatment effects generated from the IPD to project outcomes in population-level data,

Table 1. Benefits and challenges of IPDMA of ageing research trial data

Benefits of IPDMA	Challenges of IPDMA
Supports inclusion of IPD from unpublished trials, and analysis of unreported outcomes	Requires considerable time and resource for implementation, and cannot be done by a small volunteer team
Allows greater opportunity for standardising outcomes and covariate definitions	Needs a team of researchers with requisite expertise in managing and preparing IPD
Enables independent scrutiny of original trial data	Estimating how long the IPDMA will take can be difficult, because progress is not entirely under control of the research team
Supports more reliable risk of bias assessment	Obtaining funding for IPDMA can be challenging because of uncertainties in how much IPD will be available and how much time will be needed for the project
Enables application of a consistent method of analysis across trials	Obtaining ethical approval can be challenging because different requirements may be required across different countries that the IPD is requested from
Provides greater power for investigating how participant characteristics predict treatment effects	Development and approval of data sharing agreements can be time consuming, requiring agreement across multiple institutions
Can increase generalisability of findings by weighing the IPD based on population-level data	Despite all appropriate preparation, it is possible that original trialists may not agree to share IPD, or withdraw agreement at a later date
Enables discussion of implications of findings with a multidisciplinary group of researchers including original trial investigators	Potentially small number of common variables across trials and multiple outcome measures in use across different domains relevant for ageing research (for example ADL, cognition, health-related quality of life) mean that data harmonisation can be especially challenging
Supports wider dissemination of findings through collaborative networks, patient groups and the wider public	Even with access to IPD, it is possible that required data may not be available in a format suitable for the planned analysis

or a combination of both [10]. This is of particular relevance for trials involving older people, where there may be concerns that participants may not be representative of the wider older population [11].

Although IPDMA of RCTs has been well-established in many other specialty areas spanning cardiovascular disease, oncology, diabetes, infectious disease and mental health [12], the approach has not yet become widely used in ageing research. To date, the few examples of IPDMA of ageing research trials have pooled a small number of datasets from individual countries only, thereby limiting wider generalisability of findings [13, 14]. However, some of the earliest examples of IPDMA include areas of relevance for ageing research, such as the Antithrombotic Treatment Trialists Collaboration [15] and the Cholesterol Treatment Trialists Collaboration [16]. More recently, repositories of trial data have been established (or are in setup) to support IPDMA; examples include the Virtual International Stroke Trials Archive [17] and the Developing Resources and Minimum Data set for Care Homes Adoption study [18].

Challenges of IPDMA

Although IPDMA of clinical trial data offers many potential benefits, the challenges and complexities should not be underestimated (Table 1). Key challenges relate to the complexity of collecting and preparing datasets, which require a meticulous approach involving experienced researchers, frequently with expertise in designing and analysing clinical trials. Aligned with recognised good practice in clinical trials and evidence synthesis, researchers must ensure that they pre-specify hypotheses and describe all methods in a study protocol. This serves to limit bias, reduce risk of 'data dredging' and *post hoc* cherry picking of small effects that can gain statistical significance with larger sample sizes, and ensure overall transparency [19].

There may be a relatively small number of common variables across trials, with challenges related to different methods of recording data, for example gait speed, grip strength, or blood pressure. The time and resource for implementing IPDMA can be considerable, particularly the recoding and harmonisation of individual datasets as part of data preparation, and obtaining the necessary resources for secure storage of original trial data and the combined IPD dataset. It is theoretically possible to use a two-stage IPDMA whereby individual datasets are analysed at the original host site, or in a data repository (stage 1), with summary statistics subsequently combined in meta-analysis (stage 2). Typically this is infeasible in requiring considerable iterative input from the original trial investigators, a challenge for large, complex IPDMA. Future research to develop distributed algorithms that support analysis without requiring data transfer or iterative data analysis may support more efficient IPDMA [20].

Obtaining the necessary ethical approvals and data sharing agreements has challenges that require careful planning and discussion. This is a non-trivial step that is made more straightforward if consent to share trial data has been included in the original trial consent documentation. Considerable statistical input is required throughout the process, aligned with the complexities of data preparation and standardised analytic approaches. Harmonisation of trial baseline and outcome measures may be particularly challenging, given the range of instruments that may be used across the domains of, for example, cognition, ADL, nutrition and physical activity [21, 22].

Despite all appropriate preparation, it is possible that researchers may not wish to share IPD, leading to a selective

Table 2. The five stages of the processing, replication, imputation, merging and evaluation to prepare individual participant data for meta-analysis guidelines, and actions involved at each stage

Stage	Actions
1. Processing	Standardising the data to a preferred format, typically based on the statistical software package that is chosen for data manipulation. Verification of the data, recoding of variables of interest and harmonisation of scales of measurement. Checking sample size and key descriptive data is recommended as a useful initial step at this stage.
2. Replication	Replication of published data tables (e.g. baseline characteristics table) ensures that the processed datasets are consistent with the data that have been analysed for previously published reports.
3. Imputation	Imputation of missing data may be considered, depending on the stated research question, before or after merging data into a single harmonised dataset.
4. Merging	Data are merged into a single harmonised dataset.
4. Evaluation	Evaluation of data heterogeneity and distribution can then be explored prior to the planned pooled analysis, to inform selection of appropriate analytic methods.

sample of evidence [23]. Indeed, this has been problematic in dementia research, especially with industry-funded trials.

Managing and preparing IPD

The processing, replication, imputation, merging and evaluation to prepare IPD (PRIME-IPD) for meta-analysis has been developed as a concise set of guidelines to support a systematic approach to managing and preparing IPD [24]. It consists of five stages, each of which is viewed as a key step in the IPDMA process (Table 2).

Despite the challenges in obtaining, and preparing IPD for MA, a systematic review of 323 IPDMAs across different specialty areas reported that 54% obtained IPD from over 80% of eligible trials, and 87% obtained IPD from over 50% of eligible trials [25]. The 2021 United Nations Educational, Scientific and Cultural Organisation (UNESCO) Recommendation on Open Science provides strong global support for making scientific knowledge openly available, accessible and reusable [26]. Research funders and leading journals who support Open Science now expect data sharing policies to be developed to encourage responsible clinical trial data sharing, facilitating IPDMA [27, 28]. For example, the US National Institute on Aging now expects sharing of clinical trial data through a repository, and data sharing is strongly supported by the UK National Institute for Health Research (NIHR). When it is not possible to obtain IPD from all trials, established methods enable combining aggregate data from remaining trials with IPD so that the potential risk of selective samples can be determined and the overall estimates of effect can be adjusted accordingly [29].

Combining trials that use different study designs

One question that may arise is how trials with different study designs (for example individually randomised trials, cluster randomised trials and interrupted time series designs) can be combined in IPDMA. In this scenario, a two-stage IPDMA may be more straightforward. Here, the treatment effect estimate is obtained by analysing individual trials using methods that take account of trial design in stage 1, whereas the treatment effect estimates are combined in stage 2. The alternative one-stage approach, where the IPD from trials is all analysed together, is potentially more complex, as dummy variables must be used to distinguish between different trial designs.

Implications for structuring datasets in new ageing research trials

Efforts to better standardise ageing research trial measures through consensus agreement of common data elements (CDEs) could help to address some of these complexities, although retrospective harmonisation with historical trial datasets will continue to be required [30]. CDEs are a minimum standardised set of data elements that would be collected across trials, including baseline descriptors. CDEs form the basis for other data that could be collected depending on the trial phase, intervention and setting [31]. CDEs can include core outcome measures (COMs)—a minimum standardised list of outcomes to be reported. There are many challenges in developing CDEs and COMs for ageing research trials, and it can be difficult to accommodate them when designing a trial. Such practices could lead to data collection burden, whereby the amount of data to be collected for a trial is perceived as excessive, potentially resulting in declining participation, incomplete data completion or trial withdrawal [32]. Given the relative paucity of empirical evidence [33], future work should evaluate potential data collection burden while attempting to develop CDEs and COMs.

Potential applications in ageing research

IPDMA of RCT data offers a range of major potential advantages that have particular relevance for ageing research. We outline three examples describing how IPDMA could be used to stratify care for older people with frailty and to evaluate fall prevention and translational geroscience interventions. For each example, we focus on how particular characteristics can be used to investigate prediction of treatment effects to stratify care. In each example, the use of IPDMA could support investigation of whether or how treatment

effects differ according to important characteristics, such as ethnicity, sex and socioeconomic position.

Stratifying treatment by level of frailty

In general, there are two classes of analysis that frailty is important for:

- Trials seeking to prevent, reverse or mitigate against frailty itself.
- Trials in other conditions (e.g. heart failure, hypertension and diabetes) where frailty is a key covariate that can be used to establish the relative effectiveness of interventions in different subgroups.

UK and international guidelines recommend routine identification of frailty so that interventions such as resistance exercise training and CGA can be provided [34–36]. Although guideline recommendations are ideally informed through meta-analysis of RCTs of interventions, limitations of standard meta-analysis techniques mean that there are ongoing evidence gaps relating to the effectiveness of interventions for older people across the frailty spectrum. For example, there is uncertainty regarding how resistance exercise training interventions should be targeted for people with different levels of frailty because trials have not generally used standardised frailty measures to investigate how intervention effects vary by frailty severity. Furthermore, many of the CGA trials were done before established frailty measures were available, meaning that it is difficult to have certainty regarding whether CGA is equally effective across the frailty spectrum, or more or less effective for people with different frailty levels.

Although frailty identification has not historically been standardised across RCTs, most trials collect the necessary data on clinical signs/symptoms, diseases, disabilities and impairments to construct a cumulative deficit model FI. A retrospective FI has recently been derived from baseline data in an RCT of intensive glucose control and blood pressure lowering therapy [37]. Furthermore, components of the phenotype model of frailty (weight loss, exhaustion, low energy expenditure, gait speed, grip strength) have commonly been collected individually or in combination in ageing research trials. In particular, gait speed can be used as a simple instrument to identify frailty and has been widely collected in research studies [38, 39].

Collection of these IPD and standardisation of frailty measurement across trials based on generation of an FI score, phenotypic frailty measure, or single proxy for frailty such as low gait speed would be a key step in initial data preparation. A standardised FI score was used in an IPDMA of eight primary care-based trials of proactive, multidisciplinary care in the Netherlands, reporting that strategies based on frailty identification were unlikely to be cost-effective [14]. A 40 deficit FI has been implemented in an IPD meta-analysis including 19 trials of pharmacological interventions in type-2 diabetes, rheumatoid arthritis and COPD [40]. The IPDMA reported that the highest FI score was lower than the general population, highlighting the selection bias of recruiting people who are less frail than the wider population. These findings heighten a common concern that older people with conditions such as frailty and dementia are underrepresented in large scale disease-focused trials. Nevertheless, the IPDMA identified that people with a higher FI score were at greater risk of serious adverse events from treatment.

Extension of the approach across other specialty areas would provide additional valuable understanding of how the presence of frailty modifies treatment effects, remaining open to the possibility that some interventions might work best in frailer people. This is particularly pertinent given the increasing number of trials involving older people, especially in geriatric oncology and cardiology, but rarely of sufficient numbers to support useful subgroup analyses at the individual trial level. Ongoing evidence gaps could be identified with greater certainty, identifying clearer targets for future RCTs of interventions to further populate the evidence base.

Fall prevention

Falls are a major clinical and public health concern globally. Around one-third of older people experience a fall every year, with major impact on physical and mental health, and considerable cost to healthcare systems [41, 42]. Falls are the leading cause of injuries in older people and are a major contributor to disability in later life [41].

Standard meta-analysis of fall prevention intervention trial data indicates that exercise alone and in combination with other components including vision assessment and treatment, environmental assessment and modification, multifactorial assessment and treatment, and case management can reduce injurious falls [43, 44]. However, examination of characteristics of fall prevention trial participants indicates that around 90% of participants are female, with limited understanding of whether fall prevention interventions vary by sex [45]. Furthermore, although fall prevention trials have typically selected participants on the basis of some measure of falls risk (e.g. history of falls), the risk of experiencing a fall is related to many other factors (e.g. cognitive impairment, sensory impairment, polypharmacy), and it is uncertain whether fall prevention interventions are equally effective across people at different levels of predicted risk. Additionally, inconsistency in reporting of certain outcomes, including fall rates and quality of life, has prevented detailed examination of these outcomes using standard meta-analysis methods [43].

Collection and analysis of IPD from fall prevention trials could help to address some of these uncertainties and support stratified care for people at risk of falls. Pooling of IPD could enable analysis of whether intervention effects vary by gender. Replication of fall prediction models [46] in the baseline IPD could support investigation of how intervention effects vary by baseline falls risk, informing stratified fall prevention care. Use of the IPD to generate a health utility

score such as the SF6D, which is infrequently reported but can be derived from the SF36 and SF12, two common trial outcome measures [43, 47], could help to inform whether fall prevention interventions improve health-related quality of life and are cost-effective

IPDMA in translational geroscience

Geroscience seeks to understand the genetic, molecular and cellular mechanisms that make ageing a risk factor for and driver of common long-term conditions and diseases of older people [48]. Translational geroscience investigates interventions targeting these mechanisms of ageing to delay, prevent or treat age-related diseases and disabilities as a group, rather than individually. The Translational Geroscience Network is a multi-institution collaboration of US researchers studying clinical interventions targeting mechanisms of ageing [49].

There is considerable potential for using IPDMA in translational geroscience, supporting investigation of how particular genetic, molecular and cellular mechanisms predict response to treatments. An area of particular relevance is investigation of senolytic drugs, which selectively clear senescent cells that accumulate with ageing and are viewed as a root-cause contributor to many late-life diseases and common conditions [50]. Ongoing clinical trials of senolytic drugs span key areas including Alzheimer's dementia, osteoporosis and osteoarthritis. Future use of IPDMA could support targeted use of senolytics based on better understanding of how ageing biomarkers predict treatment effects, taking into account the balance of effectiveness, tolerability and potential toxicity at individual level.

IPDMA training

A range of training courses and resources for IPDMA are available. A useful starting point is the website ipdma.co.uk [51], which provides an overview of IPDMA, guidance and methods, statistical software and code, and links to courses and additional resources, including the IPDMA handbook for healthcare research [52]. The Cochrane IPDMA Methods Group website is another useful resource, providing practical guidance and links to relevant training courses [53]. Topics covered include important additional aspects of IPDMA, for example assessment of risk of bias, application of Grading of Recommendations Assessment, Development and Evaluation in IPDMA, and approaches to missing data.

Ageing research trialists collaborative

IPDMA of RCTs would be facilitated by an international collaborative of trialists with a shared interest in a particular research area. Without their participation and sharing of original trial data, there would be no data to analyse for IPDMA. The considerable efforts of trial teams and participants, as part of original trial implementation and analysis, should be fully recognised and acknowledged as a critical part of the IPDMA.

In anticipation of future IPDMA work in ageing research, we are therefore establishing an international Ageing Research Trialists (ART) collaborative. The main objectives of the ART are summarised in Box 1. We anticipate that the establishment of this international collaborative will be a critical step in supporting IPDMA in ageing research.

Conclusions

The use of IPDMA of ageing intervention trial data has potential to transform understanding of how interventions should be targeted for those who are most likely to benefit from them, offering major advantages over standard meta-analysis using aggregate data. Key potential applications of IPDMA of ageing research trials include investigation of how key characteristics predict treatment effects of interventions, identifying which groups experience most benefit, and whether some groups are more likely to experience no benefit, or indeed harm. Using IPDMA to evaluate how intervention effects vary according to gender, ethnicity and sociodemographic factors additionally offers insight into potential health inequalities in care for older people.

Obtaining funding for IPDMA may be challenging as considerable resource is required to obtain and prepare IPD, and research funders may have legitimate concerns regarding obtaining sufficient IPD for useful analysis as part of individual research projects. The collection and preparation of IPD for meta-analysis should be viewed as the establishment of research data infrastructure, and appropriate resources should be sought from a range of research funding sources to support this. The 2021 UNESCO Open Science recommendations align closely with the vision for IPDMA, lending influential global support for efforts to make scientific knowledge openly available, accessible and reusable.

The establishment of an international ART collaborative is a key initial step in supporting future IPDMA in ageing research. This includes ensuring that appropriate recognition is given to individual trial teams who support IPDMA, recognising that generated IPD datasets should be viewed as a wider resource for future research to improve care for older people as a shared ambition across nations.

Box 1. Main objectives of the international ART collaborative.

- To provide support for the synthesis of international ageing research trial datasets for IPDMA, including obtaining funds for managing, preparing and analysing data in secure research environments with the necessary safeguards.
- To prospectively plan IPDMA of ageing research trials in key areas of international importance, helping

reduce possible bias once ongoing and new trials have published findings.
- To ensure that, as far as possible, the generated IPD datasets are made available to the wider scientific community for secondary analysis.
- To provide scientific review of proposals for analysis of generated IPD datasets, ensuring proposals are novel, of sufficient quality and that appropriate recognition is given in any academic outputs to the research teams who provided original trial data for the IPD.
- To support the development of early career ARTs, for example by encouraging trialists who are sharing data for IPDMA to include early career researchers in the project team where appropriate.
- To encourage ARTs to standardise collection of baseline measures and outcomes, and develop trial data management plans that support data sharing for IPDMA.
- To promote best statistical practices in the analysis of IPDMA data.

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References

1. World Health Organisation. Decade of Healthy Ageing 2021-2030: Plan of Action. United Nations, New York, US 2020.
2. Medical Research Council (2018) The MRC Framework for the Development, Design and Analysis of Stratified Medicine Research. Swindon, UK: Publisher: Medical Research Council. ISBN: 978-0-903730-28-0 https://mrc.ukri.org/research/initiatives/stratified-medicine/stratified-medicine-methodology-framework/
3. Hingorani AD, Windt DA, Riley RD *et al.* Prognosis research strategy (PROGRESS) 4: stratified medicine research. BMJ 2013; 346: e5793.
4. European Science Foundation Forward Look. Personalised Medicine for the European Citizen. In: Holgate ST, Palotie A, Prainsack B. (eds), Towards more Precise Medicine for the Diagnosis, Treatment and Prevention of Disease. Strasbourg, France: ESF, 2012; 13–17.
5. National Research Council 2011. Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. Washington, DC: The National Academies Press. https://doi.org/10.17226/13284
6. Denny JC, Collins FS. Precision medicine in 2030-seven ways to transform healthcare. Cell 2021; 184: 1415–9.

7. Geissbuhler M, Hincapie C, Aghlmandi S, Zwahlen M, Juni P, da Costa B. Most published meta-regression analyses based on aggregate data suffer from methodological pitfalls: a meta-epidemiological study. BMC Med Res Methodol 2021; 21: 123.
8. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Chichester, UK: Cochrane, 2021. Available at www.training.cochrane.org/handbook
9. Schmid C, Stijnen T, White I. Handbook of Meta-Analysis. London, UK: CRC Press, 2021.
10. Stuart EA, Ackerman B, Westreich D. Generalizability of randomized trial results to target populations: design and analysis possibilities. Res Soc Work Pract 2018; 28: 532–7.
11. Sheppard JP, Lown M, Burt J *et al.* Generalizability of blood pressure lowering trials to older patients: cross-sectional analysis. J Am Geriatr Soc 2020; 68: 2508–15.
12. Tierney J, Stewart L, Clarke M: Individual participant data (Chapter 26). In: Higgins J, Thomas J. (eds), Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021) Chichester, UK.: Cochrane, 2021. Available at www.trainingcochraneorg/handbook
13. Blom J, den Elzen W, van Houwelingen AH *et al.* Effectiveness and cost-effectiveness of a proactive, goal-oriented, integrated care model in general practice for older people. A cluster randomised controlled trial: integrated systematic care for older people–the ISCOPE study. Age Ageing 2016; 45: 30–41.
14. Blom JW, Van den Hout WB, Den Elzen WPJ *et al.* Effectiveness and cost-effectiveness of proactive and multidisciplinary integrated care for older people with complex problems in general practice: an individual participant data meta-analysis. Age Ageing 2018; 47: 705–14.
15. https://www.ctsu.ox.ac.uk/research/att (2 February 2022, date last accessed).
16. https://www.ctsu.ox.ac.uk/research/ctt (2 February 2022, date last accessed).
17. https://www.virtualtrialsarchives.org/vista/ (2 February 2022, date last accessed).
18. https://dachastudy.com (2 February 2022, date last accessed).
19. Tierney JF, Vale C, Riley R *et al.* Individual participant data (IPD) meta-analyses of randomised controlled trials: guidance on their use. PLoS Med 2015; 12: e1001855.
20. Duan R, Luo C, Schuemie MJ *et al.* Learning from local to global: an efficient distributed algorithm for modeling time-to-event data. J Am Med Inform Assoc 2020; 27: 1028–36.
21. Fortier I, Raina P, Van den Heuvel ER *et al.* Maelstrom research guidelines for rigorous retrospective data harmonization. Int J Epidemiol 2017; 46: 103–5.
22. Fortier I, Doiron D, Little J, Ferretti V, L'Heureux F, Stolk RP, Knoppers BM, Hudson TJ, Burton PR, International Harmonization I: Is rigorous retrospective harmonization possible? Application of the DataSHaPER approach across 53 large studies. Int J Epidemiol 2011, 40: 1314–28.
23. Riley RD, Ensor J, Snell KI *et al.* External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges. BMJ 2016; 353: i3140.
24. Dewidar O, Riddle A, Ghogomu E *et al.* PRIME-IPD SERIES part 1. The PRIME-IPD tool promoted verification and standardization of study datasets retrieved for IPD meta-analysis. J Clin Epidemiol 2021; 136: 227–34.
25. Wang H, Chen Y, Lin Y, Abesig J, Wu IX, Tam W. The methodological quality of individual participant data meta-analysis on intervention effects: systematic review. BMJ 2021; 373: n736.
26. UNESCO Recommendation on Open Science. United Nations Educational, Scientific and Cultural Organisation. United Nations, 2021; In.
27. Mello MM, Francer JK, Wilenzick M, Teden P, Bierer BE, Barnes M. Preparing for responsible sharing of clinical trial data. N Engl J Med 2013; 369: 1651–8.
28. Naudet F, Sakarovitch C, Janiaud P *et al.* Data sharing and reanalysis of randomized controlled trials in leading biomedical journals with a full data sharing policy: survey of studies published in the BMJ and PLOS medicine. BMJ 2018; 360: k400.
29. Riley RD, Simmonds MC, Look MP. Evidence synthesis combining individual patient data and aggregate data: a systematic review identified current practice and possible methods. J Clin Epidemiol 2007; 60: 431–9.
30. Lutomski JE, Baars MA, Schalk BW *et al.* The development of the older persons and informal caregivers survey minimum DataSet (TOPICS-MDS): a large-scale data sharing initiative. PLoS One 2013; 8: e81673.
31. Muscedere J, Afilalo J, Araujo de Carvalho I *et al.* Moving towards common data elements and Core outcome measures in frailty research. J Frailty Aging 2020; 9: 14–22.
32. Ulrich CM, Wallen GR, Feister A, Grady C. Respondent burden in clinical research: when are we asking too much of subjects? IRB 2005; 27: 17–20.
33. Naidoo N, Nguyen VT, Ravaud P *et al.* The research burden of randomized controlled trial participation: a systematic thematic synthesis of qualitative evidence. BMC Med 2020; 18: 6.
34. Turner G, Clegg A, British Geriatrics S, Age UK. Royal College of general P: best practice guidelines for the management of frailty: a British Geriatrics society, Age UK and Royal College of general practitioners report. Age Ageing 2014; 43: 744–7.
35. Morley JE, Vellas B, van Kan GA *et al.* Frailty consensus: a call to action. J Am Med Dir Assoc 2013; 14: 392–7.
36. Dent E, Morley JE, Cruz-Jentoft AJ *et al.* Physical frailty: ICFSR international clinical practice guidelines for identification and management. J Nutr Health Aging 2019; 23: 771–87.
37. Nguyen TN, Harris K, Woodward M *et al.* The impact of frailty on the effectiveness and safety of intensive glucose control and blood pressure-lowering therapy for people with type 2 diabetes: results from the ADVANCE trial. Diabetes Care 2021; 44: 1622–9.
38. Graham JE, Ostir GV, Fisher SR, Ottenbacher KJ. Assessing walking speed in clinical research: a systematic review. J Eval Clin Pract 2008; 14: 552–62.
39. Clegg A, Rogers L, Young J. Diagnostic test accuracy of simple instruments for identifying frailty in community-dwelling older people: a systematic review. Age Ageing 2015; 44: 148–52.
40. Hanlon P, Butterly E, Lewsey J, Siebert S, Mair FS, McAllister DA. Identifying frailty in trials: an analysis of individual participant data from trials of novel pharmacological interventions. BMC Med 2020; 18: 309.

41. Public Health England. Falls: Applying All Our Health. London, UK: Public Health England, 2020.
42. Burns ER, Stevens JA, Lee R. The direct costs of fatal and non-fatal falls among older adults - United States. J Safety Res 2016; 58: 99–103.
43. Tricco AC, Thomas SM, Veroniki AA *et al.* Comparisons of interventions for preventing falls in older adults: a systematic review and meta-analysis. JAMA 2017; 318: 1687–99.
44. Sherrington C, Fairhall N, Wallbank G *et al.* Exercise for preventing falls in older people living in the community. Cochrane Database Syst Rev 2019; 1: CD012424.
45. Ng C, Fairhall N, Wallbank G, Tiedemann A, Michaleff ZA, Sherrington C. Exercise for falls prevention in community-dwelling older adults: trial and participant characteristics, interventions and bias in clinical trials from a systematic review. BMJ Open Sport Exerc Med 2019; 5: e000663.
46. Gade GV, Jorgensen MG, Ryg J *et al.* Predicting falls in community-dwelling older adults: a systematic review of prognostic models. BMJ Open 2021; 11: e044170.
47. Contopoulos-Ioannidis DG, Karvouni A, Kouri I, Ioannidis JP. Reporting and interpretation of SF-36 outcomes in randomised trials: systematic review. BMJ 2009; 338: a3006.
48. https://www.nia.nih.gov/research/dab/geroscience-interse ction-basic-aging-biology-chronic-disease-and-health (22 December 2021, date last accessed).
49. https://www.gerosciencenetwork.org (22 December 2021, date last accessed).
50. Kirkland JL, Tchkonia T. Senolytic drugs: from discovery to translation. J Intern Med 2020; 288: 518–36.
51. Individual Participant Data Meta Analysis. https://www.ipdma.co.uk/training-courses (1 February 2022, date last accessed)
52. Riley RD, Tierney JF, Stewart LA. Individual Participant Data Meta-Analysis: A Handbook for Healthcare Research. Wiley, Chichester, UK. 2021
53. The Cochrane Collaboration. Cochrane IPD Meta Analysis Methods Group. https://methods.cochrane.org/ipdma/ (1 February 2022, date last accessed)

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