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

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Invited Opinion

Clinical studies in the elderly – Why and how should we care?

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The elderly represent the fastest growing group in the age pyramid, particularly in industrialized countries. Such a demographic shift represents an enormous societal challenge and a significant burden for healthcare systems. The health challenges posed by the elderly vary with age, necessitating the need to stratify elderly cohorts into subgroups, e.g. 65–74, 75–84 and ≥85 years old. Such grouping acknowledges the fact that, persons over the age of 75 generally show greater frailty, a condition characterized by serious mental and physical weaknesses.

Despite the changing demographic, efforts to develop novel drugs and non-pharmacological interventions for age-related ailments of the brain have been largely neglected or abandoned. The latter includes potential treatments for neurodegenerative disorders, arguably the most urgent, but also competitive, area. Currently, promising results are emerging from early-life preventive interventions. While these will likely extend the period of disease-free life, the quest for innovative interventions for maintaining or improving brain health among the elderly must be pursued with greater energy and resources and must be in accord with the highest standards of clinical research.

Besides dividing cohorts of elderly persons into defined sub-groups, clinical researchers should also consider other important variables such as sex, race and ethnicity. As recently exemplified by vulnerability to the SARS-CoV-2 pandemic, these factors are important modifiers of susceptibility and treatment response in systemic diseases (e.g. metabolic, cardiovascular, immune, skeleto-muscular) as well as disorders of the brain (e.g. mood, anxiety, stroke, dementia). It is crucial that investigators appreciate that it is unlikely that the results of research on a homogenous group will extrapolate to other sub-populations; study designs, as well as the interpretation of results, should include systematic evaluation of distinct risk-benefit ratios.

The elderly consume about one third of all medicines, making the evaluation of new drugs in the elderly an important issue. Currently, data on clinical efficacy and safety in the elderly is required by regulators for registration, unless a drug is unlikely to be used in aged individuals. It is, however, important to note that clinical study designs involving senior participants should consider age-related changes in physiology such as reduced liver and renal function (which impact on the absorption, distribution, metabolism and excretion of drugs) in order to explain any variation in efficacy of therapeutic interventions in differently- aged subjects. Also, to be kept in mind is that age-related pharmacokinetics and pharmacodynamics, together with co-morbidities and concomitant medications may render geriatric patients more prone to adverse effects. In brief, inclusion of elderly subjects in efficacy-safety studies will facilitate use of the population approach to explore pharmacokinetic variability and associated altered clinical outcomes.

An additional aspect that needs to be mentioned with respect to clinical investigations of the central nervous system (CNS) is that of altered sensitivity to certain compounds as a function of age. For example, there is an increase in sensitivity to some drugs (e.g. antipsychotics, due to the age-related increase in monoamine oxidase activity). Other important considerations that must be taken into account in clinical research on the aging brain are reduced cerebral blood flow and atrophy in many older

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Table 1
The principles of ICH GCP (from https://ichgcp.net).

1	Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2	Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3	The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4	The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5	Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6	A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.
7	The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8	Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9	Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10	All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11	The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12	Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13	Systems with procedures that assure the quality of every aspect of the trial should be implemented.

persons. The latter may be more pronounced in some brain regions/systems than in others; as an example, anticholinergic drug effects may be exacerbated because of an age-related loss of cholinergic neurons. Further, elderly persons are more likely to suffer from a dementia, Parkinson's disease, urinary incontinence, diseases of the ear and eye, sleep disorders and depression as well as one or more components of the metabolic syndrome, especially diabetes and hypertension. All of these considerations need to be factored into the design of properly controlled clinical studies in the elderly, be they pharmacological interventions and/or (neuro)psychological and technological interventions. Moreover, efficacy of any given intervention should be based on a broad range of outcomes – from psychological, cognitive, and biomarker measurements to quantifiable indices of quality of daily living; this will allow assessment of health gains after adjustment for age.

While the benefits of including older subjects in clinical research are many for the aging population at large and healthcare producers and providers alike, the scientific, ethical and regulatory principles that ~~be~~ guide clinical trials in younger individuals be must be equally adhered to in studies on the elderly. In addition to demonstrating awareness of their distinct physiological and pathophysiological characteristics, clinical research on the elderly must not lose sight of individuals' particular family and social circumstances that can profoundly affect treatment compliance and outcomes. This inevitably means that, to keep with the latest standards of clinical research, the study design process must i) ultimately demonstrate the efficacy and safety of a given intervention for a specific group of persons (in our case, aging individuals); ii) must address the applicability of the intervention even in the presence of comorbidities; and iii) must involve sufficiently large cohorts to allow statistical validation and identification of particular subgroups that will respond positively or adversely to the intervention. It is only by following this strategy that we can consolidate clinical data so as to improve the prospects of maintaining brain health in the old and very old. *Aging Brain* advocates for this all-embracing approach in clinical studies, thus complying with the good clinical practice (GCP) principles summarized by the International Conference on Harmonization (ICH) of the GCP network (see Table 1).

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