Including the Elderly in Clinical Trials – a Regulatory Viewpoint

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ANY OPINIONS EXPRESSED IN THIS PRESENTATION ARE MY OWN, ARE NOT NECESSARILY SHARED BY OTHER ASSESSORS AT THE MHRA, AND CAN NOT BE CONSIDERED TO BE UK POLICY

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STUDIES IN SUPPORT OF SPECIAL POPULATIONS: GERIATRICS E7

Current *Step 4* version

dated 24 June 1993

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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E7 Studies in Support of Special Populations: Geriatrics

Questions & Answers

Current version

dated July 6, 2010

Many clinical trials exclude patients aged > 65 to 70 years old.

Consequently, evidence and knowledge about responses of geriatric patients to medications is inadequate, hindering understanding of the benefit-risk profile of drugs in this population.

While Phase I trials may not necessitate representation of older adults with high risk complications, the enrolment of older adults in Phase II and III clinical trials is essential to achieve the goal of confirming dosage, safety, adverse events and effectiveness.

Why do we need an adequate representation of geriatric patients in the clinical database?

Geriatric patients can respond differently from younger patients to drug therapy in a number of ways and such differences can be greater in patients 75 years and older.

The geriatric population has age-related physiological changes that can affect the pharmacokinetics (PK) of the drug, and the pharmacodynamic (PD) response to the drug, both of which can influence the drug-response and the dose response relationship.

Geriatric patients are more prone to adverse effects since they often have co-morbidities and are taking concomitant therapies.

With the increasing size of the geriatric population (including patients 75 and older) and in view of the recent advances in PK and PD, the importance of geriatric data (from the entire spectrum of the geriatric patient population) in a drug evaluation programme has increased.

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How big a problem is this?

A cross-sectional, structured review of publicly available initial approval documents of Food and Drug Administration-approved drugs was performed (Ruiter R, Burggraaf J, Rissmann R. *Br J Clin Pharmacol*. 2019;85(4):838-844). Based on the available initial approval documents, it was concluded that 62, 42 and 45% of the FDA documents included reports on pharmacokinetic, safety and efficacy analyses, respectively, in the elderly.

However, data also showed that only 15% of clinical trial participants for drugs were 65 and older.

Why is this still happening?

	Healthy subjects	Patients
PROs	• Easier and quicker recruitment and management in the clinical unit, resulting in more efficient study • No confounding pathology or medications • Easier to obtain blood for full PK profile • Data may be useful for several indications • Wide choice of potential FIH sites and investigators • High internal validity	• PD/biomarker and surrogate data may only be obtainable in patients • Target-related safety may be tested • Possible benefit, especially at higher doses (oncology settings) • High external validity
CONs	• Often no or limited target-related PD/biomarker data obtainable • Often difficult to justify target availability in healthy subjects (but may be expressed at low levels) • Target-related safety may be different from patients (but off-target toxicity likely to be similar) • PK may be different from patients • No therapeutic benefit to subjects, only potential risks • Low external validity	• Recruitment and management often more difficult, resulting in less efficient study (e.g. extended timelines and higher costs) • Sites that have the patients may have no experience in FIH clinical trials or facilities for extended in-house monitoring • Concomitant disorders and medications confound interpretation of safety data • Greater variability in safety signals • Target-related safety may still be different in other indications • Single dose, or low doses, may not provide adequate therapeutic benefit to justify entering very ill patients into the study, and may preclude participation in subsequent trials • Potentially more difficult to obtain blood for PK (consider sparse sampling for population PK) • Ethical concerns around placebo use

Taken from ABPI Guidelines for Phase I trials

Older people are at greater risk of side effects, and may have to drop out of a trial, creating a problem for research teams.

Older individuals may also be living alone, and may need help to interpret and comply with the trial requirements.

Older adults are at high risk for adverse drug reactions because of the PK and PD changes associated with aging. For example, hepatic and kidney function can decline in older adults, resulting in impaired absorption, excretion and metabolic clearance of drugs. Furthermore, cerebral blood flow, brain atrophy and changes in neuronal function such as cholinergic neuron loss can result in adverse drug effects on brain function (*e.g.*, cognitive abilities).

Inter-individual variability in the physiological processes increases with age.

Age is rarely an independent source of variability, but correlated with other factors such as changes in physiology that directly impact PK/PD.

Overall, older adults are more prone to adverse effects due to PK/PD changes, probable comorbidities and concomitant therapies that can interact with the investigational drug.

The adverse effects can be more severe, or less tolerated, and have more serious consequences than in the non-geriatric population.

Highly heterogeneous older patients (with diverse or wide covariate distributions) may need to be on individualised therapy, especially when the therapeutic window of a compound is narrow.

Researchers are using more population modelling now to aid the design of trial in the elderly.

Building a population pharmacokinetics model is a multi-step process. Complexity is added to the PK model as necessary.

PK/PB modelling is frequently being used to assess likelihood of DDI.

However, even without age limits, studies may bar participants who have multiple disorders or disabilities, or those with limited life expectancy or cognitive impairment.

Some researchers won’t enrol nursing home residents.

To deny older adults the opportunity of optimal or appropriate treatment due to the inadequacies of clinical trial representation, runs counter to the precepts of medical practice and could even be considered unethical.

To aid much-needed access to new treatments, EARLY clinical trials should fairly represent older adults, particularly when they are the intended recipient age group of the medication under investigation.

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One positive outcome of the COVID-19 pandemic has been the uptake of remote based clinical trials.

Such trials offer a positive step change for facilitating the appropriate inclusion of older participants, particularly for Phase II and Phase III programmes.

Conducting a clinical trial remotely allows participants to take part in research from the comfort of their own homes; with a survey supporting 74% of older adults prefer this option over in-clinic visits

(Earl *et al*. Brisbane: National Seniors 2017.)

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Remote digital monitoring technologies can be used in clinical trials to evaluate novel endpoints that provide information that was previously difficult or impossible to obtain.

These technologies could also make trials more efficient and less burdensome to participants while providing a more meaningful and complete understanding of patients' conditions and responses.

Traditional clinical trials rarely answer questions that are of greatest concern to patients, such as whether the treatment will lead to a better life. The development and availability of better endpoints and outcome measures could help meet this need.

Virtual clinical trials can be used to improve the comfort, convenience, and confidentiality for research participants compared with what they might receive in a more traditional site-based clinical trial.

The use of remote monitoring technologies is consistent at a high level with established frameworks for biomarker and clinical outcome assessment.

Virtual clinical trials should not be thought of as a separate type of trial, but as a way of thinking about trial design that meet a definition of a “quality clinical trial.”

Merely addressing the challenges that new technologies can pose, such as computer literacy, would reduce a virtual trial to its underlying technology platform.

A more important issue is whether a virtual trial allows the study to operate well from the patients' perspective.

Scientific questions, as currently framed, may seek to understand if a treatment works.

However, they may not address questions about whether the treatment will lead to a better lived experience with a disease.

Regulator’s hope that as more virtual trials are conducted and patient communities are engaged, the quality of endpoints and outcome measurements will be improved in a way that allows questions about a patient's quality of life to be better addressed.

The ICH E6 Guideline for Good Clinical Practice is, therefore, currently being revised.

The goal of this effort will be multifaceted and will include addressing the application of GCP principles to the increasingly diverse trial types and the data sources being employed to support regulatory and healthcare related decision-making on drugs, and provide flexibility whenever appropriate to facilitate the use of technological innovations in clinical trials.

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Data generated initially for healthcare purposes outside of a clinical trial or captured using innovative technological tools are being explored to serve an increasingly important role in supporting regulatory and healthcare decisions on drugs.

The application of the current standard to new technology is clearly challenging. Consequently, the design and conduct of trials may fail to take full advantage of technological innovations and the full potential of the risk-based considerations related to participant protection, data integrity or other public health considerations.

The revised guideline (planned for 2022) will provide flexibility to, among other things, accommodate the increased role of technology and variety of data sources in clinical trials.

Increased reliance on electronic systems will also necessitate updating the language in the guideline on the validity of electronic systems, documentation and signatures.

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Problem Areas and How to Resolve Them

Scientific Advice!!

Risk comes from not knowing what you're doing, Warren Buffett

That's not what I expected when I asked for advice !

The MHRA have provided scientific and regulatory advice to sponsors for many years, .

Scientific advice can be requested during any stage of the initial development of the medicinal product (before submission of a marketing authorisation application), and also during the pre-submission period for a variation to an existing marketing authorisation.

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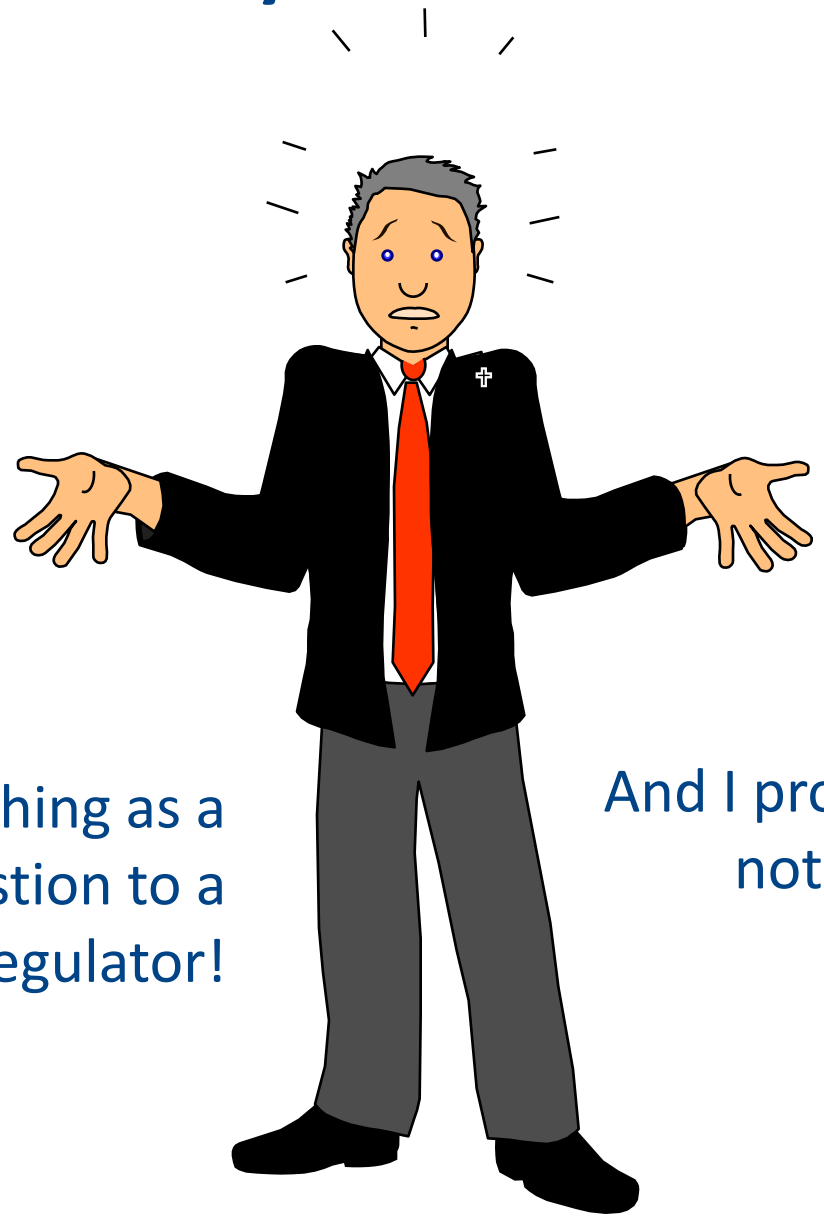
The MHRA Licensing Division held about 250 Scientific Advice meetings with Companies in 2019.

The MHRA Clinical Trials Unit has had over 100 meetings with companies, academic institutes or hospital groups over the last 8 months (many, many related to COVID-19!!)

The CTU's email helpline fields about 250 queries a month.

Any Questions ?



Don’t be shy!

There’s no such thing as a silly question to a Regulator!

And I promise I won’t take note of your names!!

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Any Further Questions ?

Please Feel Free to Contact the MHRA If You Have Any Further Queries:

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