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GUIDANCE SYNTHESIS. MEDICAL RESEARCH FOR AND WITH OLDER PEOPLE IN EUROPE: PROPOSED ETHICAL GUIDANCE FOR GOOD CLINICAL PRACTICE: ETHICAL CONSIDERATIONS

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Abstract: *Introduction:* In Europe the population is ageing rapidly. Older people are taking many medicinal products daily and these may not necessarily be suitable for them. Publications show that older patients are underrepresented in clinical trials, especially those over 75 years, with multiple co-morbidities, concomitant treatments and/or frailty. This document provides a summary of recommendations on ethical aspects of clinical trials with older people, who may in some cases be considered a vulnerable patient population. The EFGCP's Geriatric Medicine Working Party (GMWP) has developed this guidance to promote such research and to support health care professionals in their efforts. *Ethical, scope and context:* The definition of a geriatric patient is reviewed. Frail and vulnerable patients, who are a minority of geriatric patients, should be included whenever it is relevant. The legal context is described. *The process of informed consent:* All adults should be presumed capable of consent, unless proven otherwise; informed consent must be sought for all older people who are able to consent. A simple, short and easy-to-understand information sheet and consent form will contribute to improving the readability and understanding of the older participant. A participant guide and the use of a simple tool to ensure decision making capacity, are recommended. Whenever older people are unable to consent, their assent should be sought systematically using adequate information, in addition to seeking the consent of their legal or authorised representative as appropriate. *Ethics Committees:* Research ethics committees need internal and/or external geriatric expertise to balance the benefits and risks of research in older people and to appreciate and recognise their autonomy. *Design and Analyses:* Design and Analyses should be adapted to the objectives with appropriate outcomes and are not different from other clinical trials. *Conclusions:* The absence of proper recruitment or insufficient presence of older patients in clinical development plans for new medicinal products is detrimental; there is a need to improve evidence-based knowledge, understanding and management of their conditions and treatment. The aim of this guidance is to facilitate clinical research for and with the older patient population. The long version of the guidance will be available on the EFGCP's website: www.efgcp.be/.

Key words: Clinical trials and research, older people, ethics, guidance, consent, inclusion, frailty, gerontology.

Introduction

It is well recognised, that the European population is becoming increasingly aged and for many of these people the drugs used have not been specifically evaluated in this population. This document provides recommendations on ethical aspects of clinical trials performed in older people, who may in some cases be considered a vulnerable patient population.

Older people experience a higher incidence of disease-related morbidities, take more medicines with multiple medication regimes and account for more adverse drug related events than their younger counterparts. Thus, it is important to conduct more research and clinical trials in this patient population to further the understanding and management of their conditions and treatment. Medicines used by older people should be of high quality, appropriately researched and evaluated throughout their life cycles. The population included should be representative of the future consumers of the tested drugs.

History and rationale for the development of these guidance: This document is based on several workshops organised by the EFGCP GMWP, which invited J-M. Vetel and F. Hirsch to present a first draft based on the European Medicines Agency (EMA) pædiatrics guideline with the goal to foster ethical research in this neglected area.

The overall principles and key elements of this guidance were further elaborated discussed and revised by the GMWP in the following years and presented at the EMA workshop on Medicines for Older People in March 2012. Following public consultation, the GMWP has received many thoughtful comments from academia, investigators, regulators, patients advocacy groups and the pharmaceutical industry and has met twice to review and incorporate as many comments as possible into the final text. The group has shared it with all those who had contributed and/or reviewed the draft to inform them and seek their permission to mention their names.

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Ethical, Scope and Legal Context

The definition of a "geriatric patient" for use in clinical trials (UEMS-geriatric section, 2008 (1)).

Five main aspects are dominant in this definition:

- Age: "The geriatric population" is arbitrarily defined, for the purpose of this guideline, as comprising patients aged 65 years or older. It is important, however, to seek patients in the older age range, 75 and above, to the best extent possible. Protocols should not ordinarily include arbitrary upper age cut offs.
- Gender: to be representative of the geriatric general population, the proposal recommends that a majority of women should be recruited, unless there are gender specific conditions
- Functionality/ Frailty: The proposal supports the elaboration of a consensual definition of frailty, which could be used in the clinical research setting to be studied. However, additional research is needed before an operational definition of frailty can be established (2, 3).
- The number of medicines prescribed: As polypharmacy may be the consequence of multiple co-morbidities and have significant interactions itself, the registration of the number of different medications taken is a good indicator. A relatively recent overview of the literature indicates that the two most useful indicators of polypharmacy were the use of inappropriate medicines or the use of 6 and more medications at the same time (1).
- Possible exclusion criteria: in order to reflect the applicability of a particular study to use in this population the proposal is that when an exclusion criterion is proposed it must be fully justified.

The vulnerable patient

This concerns a small part of geriatric patients including frail people: Vulnerability is a condition, which represents 'Those who are relatively (or absolutely) incapable of protecting their own interests' (CIOMS. 2002 (4)) but may also reflect some more subtle issues particular to the study population.

The legal framework under which clinical trials are conducted in older patients includes regulations and guidelines for Good Clinical Practice. Research in and with the older person should comply with all relevant legal, regulatory and ethical guidelines; this includes the ICH E7 and related Q&A documents (5).

The Process of Informed Consent

The protection of older and vulnerable patients against the risks inherent in human research is paramount. However, this should not lead to exclusion of their participation and subsequent potential benefits. In many instances, older people wish to and are fully capable of participating in research.

All adults should be presumed capable of consent, unless proven otherwise: informed consent must be sought in all older people who are able to consent. A simple, short and easy-to-understand information sheet and consent form will contribute to improving the readability and understanding of the older participant, especially if it is adapted to those with a visual or other sensory impairment and is supplemented with supportive tools such as visual and hearing aids, cartoons as applicable, and a participant guide.

It is advisable to produce a specific participant guide with simple instructions and information on tests and procedures to be carried out, the need to be fasting or not, medication taken on the consultation day, return of bottles etc., contacts, end of the study or premature stopping arrangements, known &/or new safety information, publication of results etc.

Use of a simple tool or questions to check if the participant has understood the given information and implications of participation is recommended.

Assent from Older and Vulnerable Participants

Where there may be doubt that the older patient has fully understood the nature, purpose and implications of involvement in a clinical trial, it will be useful to check this matter with a simple tool (e.g. UBACC (6, 7) or Newcastle +85) (8).

Then if there is a failure to understand, their assent will not be sufficient to allow participation in that research, unless it is supplemented by the assent or consent of a proxy or the legal representative, as appropriate in that jurisdiction.

Whenever older people are unable to consent, their assent should still be sought systematically using appropriate information, in addition to the consent of their legal or authorised representative.

The consent/assent process and assessment of capacity to consent should always be performed in a supportive and caring environment with respect for patients' dignity and rights.

Ethics Committees

Research ethics committees need internal and/or external geriatric expertise to balance the benefits and risks of research in older people and to appreciate and recognise their autonomy.

All members of the research ethics committee including geriatric experts consulted on an ad hoc basis should be independent of the sponsor, the investigator and the proposed research. The qualifications and expertise of the experts used and the members of the research ethics committee should be documented and annexed to its opinion. This geriatric expertise should be available when reviewing the initial protocol and the subsequent amendments, as well as the follow-up of the study, until submission of the final report.

Design and Analyses

Design and analyses should be adapted to the research objectives with appropriate outcomes to this patient population. A comprehensive geriatric assessment could be used as criteria

for randomisation and for outcomes in designing clinical trials with specific endpoints, such as effects on cognitive function, balance and falls, urinary incontinence, &/or weight loss, as appropriate. Patients entering clinical trials, should be reasonably representative of the population that will be later treated by the drug.

Geriatric trials should be analysed for potential risks, including those that may not usually be of concern in younger people as medicines or procedures may cause adverse effects in older participants that have not been identified in young adults.

Conclusion

In Europe the population is ageing rapidly. Older people are daily taking many medicinal products, which may not necessarily be suitable for them. Publications show that older patients, especially those over 75 years, with co-morbidities, concomitant treatments and/or frailty are underrepresented in clinical trials. Direct extrapolation to older patients of efficacy/safety data and of the drug benefit/risk profile observed in younger adults is questionable and does not reflect daily life and medical practice; all of which may lead to safety issues and iatrogenic disorders. The absence of proper recruitment or insufficient presence of older patients in clinical development plans of new medicinal products is detrimental: there is a need for improving evidence-based knowledge, understanding and management of their conditions and treatment. The aim of this guidance is to facilitate clinical research in the older population. The long version of the guidance will be available on the EFGCP's website: www.efgcp.be/

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