



MEDICAL RESEARCH FOR AND WITH OLDER PEOPLE IN EUROPE

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KEYWORDS Ethics, Clinical trials, Elderly, Older people, Geriatric, Directive, Consent, Ethics Committee, Assent, Consent

EXECUTIVE SUMMARY

This document provides recommendations, primarily on ethical aspects of clinical trials performed in older people, who may belong to a vulnerable patient population.

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

While the protection against the risks of research in such a vulnerable population is paramount this should not lead to denying them the benefits of research. In many instances, older people can consent to participation in research. Should their capacity to consent be impaired for any reason, it may be advisable to make an assessment while always ensuring a supportive and caring environment respecting their dignity and rights. Whenever older people are unable to consent, their assent should be sought systematically using age appropriate information, in addition to seeking the consent of their legal or authorised representative.

Research ethics committees need internal and/or external geriatric expertise to balance the benefits and risks of research in older adults. The lack of legal ability to consent has implications on the design, analysis and the choice of comparators. Clinical trials should only be performed by investigators trained in Good Clinical Practice with experience of older patients or in collaboration with a geriatrician. Pain, fear and distress should be prevented and minimised when unavoidable. People suffering from dementia represent one of the most vulnerable geriatric populations and require even more careful review. Finally, various other aspects relating to the performance of trials in older people are discussed.

In Europe the population is ageing rapidly. Older people are daily taking many medicinal products not necessarily suitable for them. Publications show that older patients are underrepresented in clinical trials. Extrapolation from clinical trials (CT) to daily life is very difficult due to polytherapy which may lead to safety issues and iatrogenic disorders. The absence of the proper recruitment of an adequate number older patients in the clinical development plan of new medicinal products not specifically devoted to an ageing population is not ethical. The aim of this guidance is to improve this situation.

1. INTRODUCTION - RATIONALE FOR THE DEVELOPMENT OF THE RECOMMENDATIONS

The reasons why medicinal products need to be studied in older people have been detailed in various publications. Differences in pharmacokinetics and pharmacodynamics, and in adverse reactions, are more common in older people compared to adults as a whole. In comparison with younger adults, older people are characterized by age-related changes in pharmacokinetics and pharmacodynamics which, in addition to multi-morbidity and polypharmacy, increase the risk of adverse drug reactions and drug interactions.

In those cases where it is advisable to include older people in a clinical trial, the choice of subsets of the geriatric population to be included should be made on the basis of the likely target population for the medicine being tested and, the possibility of extrapolation. The scientific validity of research is not valid if the extrapolation is made from the data of younger adults. All medicines, which may be used in very old, frail or patients with multi-morbidity, should be evaluated in such patients.

Trials are necessary and should aim at progressing well-being and the treatment, prevention and diagnosis of ill health (WHO definition (1)) including for older patients.

The 1993 E7 ICH guidance from (2) Studies in Support of Special Populations: Geriatrics provides recommendations that apply for that population with the guiding principle: "Drugs should be studied in all age groups, including the elderly, 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"

In 2008 experiences from the implementation of the guidance in the ICH regions were analysed and published in a concept paper which raised requests for clarification. In 2010 ICH published (3) a question and answer document (Q&A) intended to clarify key issues.

"With the increasing size of the geriatric population (including patients 75 years and older) and in view of the recent advance in pharmacokinetics and pharmacodynamics since ICH E7 guidance was established in 1993, the importance of geriatric data (from the entire spectrum of the geriatric patient population) in a drug evaluation program has increased"

Certain specific diseases are unique to older people. Specific consequences of medical interventions may be seen in older participants. Unfortunately, this has been demonstrated by previous significant incidents with the use of medicinal products. Because of the special protection they deserve, legally incompetent older or vulnerable people should not be the subject of clinical trials when the research can be done in legally competent subjects (i.e. adults capable of informed consent). When research with older people proves necessary, the inclusion of the least vulnerable amongst them should be encouraged.

2. SCOPE

Medicinal products may be used with a view to treating, preventing or diagnosing a disease or condition. This document is also intended for all stakeholders involved in any stage of a clinical trial, including sponsors, research ethics committees, regulatory authorities, pharmaceutical companies, insurance companies and investigators (including all trial-related staff) of clinical trials conducted in older adults of all ages, their families and patient representatives. This document is applicable to interventional and non-interventional studies, and focuses specifically on geriatric clinical trials; it should therefore be read in conjunction with relevant legal texts and guidelines. Its recommendations should contribute to the promotion and protection of the dignity, the well-being and the rights of older people, who may be vulnerable and in some circumstances unable to give informed consent. Clinical trials

performed in the older population should be carried out under conditions providing the best possible protection for this vulnerable population whilst recognising their right to benefit from research.

3. ETHICAL PRINCIPLES, LEGAL CONTEXT AND FUNDAMENTAL RIGHTS

Ethical principles referred to in this document are those expressed, for example, in the Declaration of Helsinki published by the World Medical Association (2008) (4), the Charter of Fundamental Rights of the European Union (2000(5)), the Universal Declaration on Bioethics and Human Rights (UNESCO, 2005 (6)), the Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997 (7)), the International Declaration on Human Genetic Data (UNESCO, 2003 (8)), the Universal Declaration of Human Rights (1948 (9)), and the Council of Europe's Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (1997 (10)).

These principles are also echoed and referred to in the ICH E6 guideline on Good Clinical Practice (11). For the purpose of research, three ethical principles should be adhered to: **autonomy** of the participant, **beneficence** and **justice**, where autonomy means respect for a patient's autonomy and rights of dignity and privacy, beneficence is defined as the ethical obligation to do good and avoid harm, and justice is a fair distribution of burden and benefits of research. These are fully applicable to clinical trials in older patients.

3.1 LEGAL CONTEXT

The legal framework under which clinical trials are conducted in older patients includes regulations and guidelines. Research in and with the older person should comply with all relevant legal, regulatory and ethical guidelines; this includes the ICH E7 and its related Q&A document.

3.1.1 Legal context

- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 (12) on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (herein the 'Clinical Trials Directive'), as amended by
- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001(13) on the Community code relating to medicinal products for human use, as amended by
- Directive 2003/94/EC of the European Commission of 8 October 2003(14) laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.
- Regulation (EC) No 726/2004 of the European Parliament and of the Council laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. (15)
- Directive 2005/28/EC of the European Commission of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.(16)

- Pharmacovigilance regulations (EMA 2 /07/2012 (17) is comprised of Directive 2010/84/EU and Regulation (EU) No 1235/2010. (17)

3.1.2 Relevant guidelines

- Guideline for Good Clinical Practice (E 6), CPMP/ICH/135/95(11)
- Choice of Control Group in Clinical Trials (E 10), CPMP/ICH/364/96
- ICH E7 guidelines, 1993, E7 (2) 2008 Final Concept Paper (18), Q&A 2010 (3)
- CHMP Guideline on clinical trials in small populations (20),
- CHMP/EWP/83561/2005
- CHMP Guideline on conduct of Pharmacovigilance for medicines used by the geriatric population (June 2006) EMEA/CHMP/PhVWP/235910/2005- rev. 1(21)
- Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (revision 2) as required by Article 18 of Directive 2001/20/EC.(22)
- Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use (revision 1) as required by Article 8 of Directive 2001/20/EC (23).
- Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (revision 2), as required by Article 9 (8) of Directive 2001/20/EC. (24)
- Detailed guidance on the European clinical trials database (EUDRACT Database) as required by Article 11, 17 and 18 of Directive 2001/20/EC, CT 5.1 Amendment describing the Development of EudraCT Lot 1 for 1 May 2004 and CT 5.2 EudraCT core dataset.(25)
- Revised Questions and Answers on Clinical Trials (Notice To Applicants, Volume 10, April 2006 (26))
- World Health Organization, Operational Guidelines for Ethics Committees That Review Biomedical Research (Geneva, 2000 (27))
- Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). International Ethical Guidelines for Biomedical Research Involving Human Subjects (Geneva 2002 (28)).
- Management of Safety Information from Clinical Trials. Report of CIOMS Working Group VI.WHO ed. 2005 (29)

3.2 DEFINITIONS/ GLOSSARY

3.2.1 Ethics committees (and research ethics committee)

Article 2 (k) of the Clinical Trials Directive defines an ethics committee as: “An independent body in a Member State, consisting of healthcare professionals and non medical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent.” The term ‘research ethics committee’ is

increasingly used to differentiate between ethics committees specifically dealing with the conduct of research and those dealing with medical ethics in general.

3.2.2 The Geriatric Population

An European consensual definition of geriatric medicine may help to understand who the geriatric patients are.

Geriatric Medicine (accepted Malta and modified Copenhagen 2008) **UEMS-GMS definition**

Geriatric Medicine is a specialty of medicine concerned with physical, mental, functional and social conditions in acute, chronic, rehabilitative, preventive, and end of life care in older patients.

This group of patients are considered to have a high degree of frailty and active multiple pathology, requiring a holistic approach. Diseases may present differently in old age, are often very difficult to diagnose, the response to treatment is often delayed and there is frequently a need for social support.

Geriatric Medicine therefore exceeds organ orientated medicine offering additional therapy in a multidisciplinary team setting, the main aim of which is to optimise the functional status of the older person and improve the quality of life and autonomy.

Geriatric Medicine is not specifically age defined but will deal with the typical morbidity found in older patients. Most patients will be over 65 years of age but the problems best dealt with by the speciality of Geriatric Medicine become much more common in the 80+ age group

How to define a “geriatric patient” for use in clinical trials (UEMS-geriatric section, 2008 (30).

To be operational in clinical trials, this definition should be as simple as possible, reliable and pragmatic .

Five main aspects that are dominant in this definition are age, gender, function, the number of medicines prescribed and possible exclusion criteria

a. 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 extent possible. Protocols should not ordinarily include arbitrary upper age cut offs. It is also important not to exclude unnecessarily patients with concomitant illnesses; it is only by observing such patients that drug-disease interactions can be detected.

The older the population likely to use the drug, the more important it is to include the very old” [e.g. 85 and older]. (ICH E7)

b. Number of patients

“To the extent possible the enrolled patient population in clinical development program should be representative of the target patient population. As stated in the current ICH E7 guideline, estimates of the prevalence of the disease to be treated by age or examination of the age distribution of usage for other drugs of the same class or for the same indication. Given the increasing prevalence and a growing recognition of the complexity of the geriatric population, it would usually be appropriate to include more than 100 geriatric patients in the Phase 2 and 3 databases and include patients over the entire spectrum of the geriatric patient population. As single trials may not have sufficient number of geriatric patients to allow such analyses, these will often need to be carried out on pooled data.” ICH E7 Q&A 2010 (3)

The collection of necessary data may not always be possible pre authorization; in which case real life data should be collected afterwards.

c. Gender

In the group of patients with a geriatric profile, there are generally more women than men, due to the higher life expectancy of females. If there are no exclusion criteria there will automatically be more women, except for Phase 1 trials and some special cases (for example prostate problems).

The proposal should be that the majority of subjects included may be women (except for specific cases, when specific “male pathology”).

d. Functionality/ Frailty

The practical identification and definition of frailty or functional status with figures for statistical purposes, is much more complex, and there is currently no universal definition. Additional research is needed before an operative definition of frailty can be established’ (31).

The proposal should be that there is agreement on the usefulness of defining frailty in clinical settings as well as on its main dimensions, aiming at uniformity of regulatory requirements.

e. Number of medicines prescribed

As polypharmacy is the consequence of multiple co-morbidities, the registration of the number of different medications taken is a good indicator of the number of important co-morbidities. In many protocols the fact that a patient is taking 6 or more different medications may be seen as an indicator of risk of loss of autonomy and may reflect on frailty as well. A relatively recent overview of the literature indicates that the two most common indicators of polypharmacy were the use of inappropriate medicines or the use of 6 and more medications at the same time (30). The number of forbidden concomitant medicines should be minimized and limited to the number of drugs that really interact with the study drugs.

f. Exclusion criteria

Many trials include an extended list of exclusion criteria, which may not be fully justified. In fact many trials are unrealistic and do not reflect the reality of everyday practice in medicine today. The proposal is to provide justification when an exclusion criterion is proposed.

g. The vulnerable patient

This concerns a small part of geriatric patients including frail patients: Vulnerability is a condition, which represents ‘Those who are relatively (or absolutely) incapable of protecting their own interests’ (CIOMS. 2002 (28))

3.3 THE PROCESS OF INFORMED CONSENT

3.3.1 The definition of informed consent

Article 2(j) of the Clinical Trials Directive defines informed consent as follows: “A decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional

cases, as provided for in national legislation.” The witness referred to in this definition should be formally independent of the sponsor and the investigator. There is a need to clearly record the names and sufficient details of their relationship to the older patient of all persons involved in informed consent. In these recommendations, “consent” refers only to the legal definition of consent.

Of course, 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 visual and hearing aids and cartoons as applicable.

Using a simple tool or questions to check if the participant has understood the given information is recommended. Under these conditions, If this tool is used, additional informed consent is not required from a legal representative (if any), although an older patient may still be vulnerable and require additional discussions and explanations.

3.3.2 Informed consent from the legal representative, surrogate, caregiver or “personne de confiance” as in France, or “Consultee” as in the UK

When a patient is suffering from dementia for example, and is unable to provide consent, informed consent must be sought from the legal representative. Information should be given by an experienced investigator, or an adequately trained delegate, to the legal representative, on the purpose of the trial and its nature, the potential benefits and risks, and the name of the investigators(s) who are responsible for conducting the trial with background professional information (such as training and work experience) and direct contact details (telephone and e-mail) for further information regarding the trial. The legal representative should be given sufficient time and necessary information to consider the benefits and risks of involving his protected patient in the clinical trial.

When providing such information, it is important to take into consideration all the concerns of such a legal representative, especially if inexperienced with respect to the older patient’s condition. The legal representatives might therefore need more detailed and explicit information, and hence more time, to reflect on the implications of consenting, especially since they bear full responsibility for the older patient, unlike in other trials where one takes the responsibility for oneself.

Regarding the information given to the legal representatives, items for review by the research ethics committee are set out in Annex 2.

The investigator when seeking informed consent should not put undue pressure on the legal representative. For example:

In the complex relationship between legal representative and physician(s), especially in the case of chronic diseases, but also in acute serious illnesses, or in the situation where the legal representative is unfamiliar with the pattern of disease, or research into its better treatment, there is the risk that the legal representative might not fully appreciate the implications of giving consent. However, the investigator should not take part in the decision-making, but should ensure that the information has been understood and that there has been enough time allowed to come to a decision.

It is particularly important that there is no therapeutic misconception.

3.3.3 Informed consent of a patient or his/her legal representative (if any) from a patient from a different cultural background

Where appropriate, a cultural mediator, familiar with medical terminology, independent from the sponsor and investigator, experienced in the language, social habits, culture, traditions, religion and particular ethnic differences should be available in the process of obtaining informed consent.

If research takes place with patients/ groups of patients with limited command of the local language, the consent form should be translated into their mother tongue. For those with poor literacy, the use of pictorials and/or relevant communication support might be useful.

It is also important to be aware of potential cultural coercion either in a positive or negative direction and to respect the participants' privacy and dignity at all times.

3.3.4 Consent at the beginning of a trial and continued consent and assent during a trial

As for all participants, investigators should devote sufficient time to provide information and seek the older patient's assent, in accordance with legislation. It is important to realise that consent is a dynamic, continuous process, and should therefore not only be obtained prior to enrolling an older patient into a trial but should be maintained during the trial on a continuous basis. This could be done for example, by a brief discussion during each repeat visit. This process should be documented in the medical records or equivalent. The discussion is part of the ongoing dialogue between the older patient, the legal representative and the investigators and should focus on all aspects of the trial but in particular on any new information that arises in relation to the trial and that might affect the willingness of the older impaired patient or his legal representative if any to continue. Especially in long-term trials, the investigator should check the understanding of the older patient and the ability for assent. In the rare event of a change of legal representative during the trial, informed consent should be sought again as soon as possible.

3.3.5 Withdrawal of consent

Older research participants/patient and legal representatives (when applicable) should be made aware of their right to refuse to take part in a clinical trial. They should be reassured that the withdrawal from the trial will not prejudice their future treatment in any way. In addition, refusal to give consent or withdrawal of consent to participation in research must not lead to any liability or discrimination (e.g. with regard to insurance) against the person concerned.

Older patients/participants and legal representatives (when applicable) should have the opportunity to follow research as it proceeds (unless it is clinically inappropriate or it breaches the participant's right to privacy), so as to be able to decide whether to withdraw the older patient from the research at any time. In the event of withdrawal from a blinded trial, if the patient/participant or his legal representative wishes to continue to follow the progress of the trial, information should be given that the actual data will not be available until the trial has ended. When consent is withdrawn during a procedure, for example, during anaesthesia, it may not always be possible to stop the procedure immediately, as this might jeopardize the health of the older patient.

It must be emphasised that after an older patient/research participant withdraws from a trial, the investigator is still responsible for reporting trial-related events, in accord with pharmacovigilance legislation.

3.4 ASSENT FROM OLDER AND VULNERABLE PARTICIPANTS

3.4.1 Definition of assent

The notion of assent is recognised in the Declaration of Helsinki: “When a potential subject who is deemed legally incompetent, is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject’s dissent should be respected.”

3.4.2 The legal representative of older participants

In this document, therefore, the notion of legal representative should be understood to be the legally authorized representative(s), as defined in Member States’ national laws, who consent(s) on behalf of older patients recruited for research when applicable. The exact role and responsibilities of the representative in a research setting will be country specific which needs to be recognised in the clinical trial protocol and is especially important in multinational studies.

Some authors use ‘**knowing agreement**’ to reflect the outcome of the process of providing appropriate information, obtaining assent, and whenever possible obtaining written confirmation from the older subject. The capacity of an older patient to make voluntary, informed decisions, i.e. to assent, depends on the current mental capacity of the patient and his or her previous experience of life and illness.

The notion of “**presumed will**” enables legal representatives to express their duty to protect the interests of older persons, based on their experience with such persons during that person’s life up to that time.

The evaluation of whether or not an older patient can give assent should never be based on chronological age, but should depend on other factors such as intellectual capacities. This needs to be made after discussion by the legal representative with the investigator, but the legal representative will normally know the older patient better than will the investigator and hence is usually in a position to decide on whether the older patient has understood the information as much as is possible.

Older patients must participate in the consent process together with the family, caregiver and legal representative.

Involving older persons in discussions and the decision-making process respects their dignity and life experience. This process should be conducted with enough time and with a clear and short information note.

At the same time as obtaining consent from the legal representative (if any), the assent or willing agreement of the older patient must be sought. The central role of the legal or authorised representative in the protection of the older patient should be recognised. The family or proxy or the legal representative (if any) might also wish to discuss with the older patient on their own, after having been informed about the trial, and before meeting with the investigator.

If the older patient’s assent is not obtained, it is recommended that this be documented with justification in the consent form, which is signed by the legal representative and the investigator.

Where it is doubtful that the older patient has fully understood the purpose and implications of involvement in a clinical trial or research project, according to GCP recommendation, **it will be useful to use a simple tool to check** the patient’s capacity to consent (e.g. UBACC (31) or Newcastle +85) (32).

Then if there is a failure to understand, the older patient's assent will not be sufficient to allow participation in that research unless it is supplemented by the informed consent of a proxy or of the legal representative if any.

This is especially important in long term studies where changing intellectual function may occur with time and other co-morbidities.

The assent information sheets and assent forms should be appropriate and should include provision of information on the purpose of the trial, and potential benefits and harms, in terms that are honest. See also Annex 3 for recommended contents.

As discussed above, assent, like consent, is a continuous process and should be sought during the trial as well, e.g. during repeat trial visits. The wishes of older patients should be respected and they should not be expected to provide reasons for refusing to assent.

They should be informed that they may freely withdraw from the trial, at any time and for any reason, without any disadvantage or prejudice.

The processes for informing the older patient and seeking assent should be clearly defined in advance of the research and documented for each such patient. While assent may not be possible in all patients or in all research conditions (e.g., research in emergency situations), the information process provided to older patients and their response should be documented.

Every effort should be made to understand and respect differences of opinion between an older patient and his/her legal representative. Objections by an older patient must be respected.

During the Study

It is advisable to **produce a "Participant guide"** with simple instructions in concise sections and a diary with dates of visits with appropriate information and reminders; such as:

- Tests and procedures to be carried out (medication given, examination, blood tests, etc, etc) but avoid information overload.
- The need to fast or not.
- The need to take study medication or not on the consultation day.
- The presence of a carer or not.
- The return of bottles or packaging (empty or not).
- The phone number of the study assistant or secretary.
- An explanation about what will happen at the end of the study or in case of premature stopping, adverse event, new safety details, publication of results etc etc.

3.5 THE COMPOSITION OF THE ETHICS COMMITTEE IN GERIATRIC TRIALS

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 research proposed. The qualifications and expertise of the experts used and the members of the research ethics committee should be documented and annexed to its opinion. 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.

Research ethics committees specialised in geriatrics could be considered for the evaluation of trial protocols that are complex or in serious geriatric diseases. Such committees normally also include laypersons, some of whom may be representatives from the civil society.

3.5.1 Examples of geriatric expertise

Geriatric expertise goes beyond having professionally worked with older patients and could be defined on the basis of education, training and experience in the various aspects of ageing, ethics and psychosocial aspects. Therefore, this would include i) physicians with geriatric qualifications; ii) geriatric ethicists; iii) geriatric pharmacologists; iv) qualified geriatric nurses or psychologists, etc. In addition to their qualifications, it is recommended that the experts demonstrate at least some years of experience in geriatric care and direct experience of clinical trials with older patients in similar age groups, for example as an investigator in several trials performed in the older patient of similar age groups. If this cannot be found in one individual, two or more geriatric or gerontologist experts could contribute to the expertise needed. Expertise used should be documented and recorded by the research ethics committee.

3.5.2 Opinion on the protocol

The opinion will be based on, the following points :

- The need to investigate the particular indication/therapeutic to prevent the generation of area/disease, in order useless or redundant data.
- Whether the trial replicates similar trials based on an identical hypothesis (which should be avoided)
- That the protection and safety of any older patient is ensured, including minimisation of risks, fear, pain and distress, and that appropriate geriatric expertise is available at all trial sites.
- Justification is provided for the inclusion of the older patient to achieve the trial objectives.
- That appropriate non-clinical data are available before the use of the product in older patients. This may include data from old animal studies, modelling or other predictive studies.
- Whether there is an extensive and comprehensive review of available evidence (including relevant publications). Any experimental work on the investigational medicinal product should be available and reviewed to justify the initial hypothesis, the safety and the evaluation of expected benefit. The difference expected versus comparators should be described.
- The quality of the performance of the trial is such that it is likely that the results will be interpretable; monitoring, audit and quality assurance are described.
- When justified an independent Data and Safety Monitoring Board (DSMB) with appropriate expertise should be planned consistent with regulatory guidelines..
- There are provisions in the protocol for systematic independent publications of results, within a reasonable timeframe, including when results are unfavourable.
- The protocol includes provision of the medicinal products to patients involved in trials after the completion of the trial where appropriate, unless the benefit to risk balance of the medicinal product tested proves negative.
- The research ethics committee and the competent authority should ensure that the sponsor regularly monitors and re-examines the balance of benefit/risk of the research so that the health and well being of the older and vulnerable people enrolled are safeguarded.
- For randomised trials there should be equipoise (“genuine uncertainty within the expert medical community [...] about the preferred treatment”) at the beginning of the trial and no participants should receive care known to be inferior to existing

treatments. To help research ethics committees in reviewing geriatric trials, Annex 2 provides a list of the aspects to be taken into consideration when reviewing a clinical trial to be performed in the older and vulnerable population.

4. THE DESIGN OF CLINICAL TRIALS CONDUCTED WITH THE GERIATRIC POPULATION

4.1 DESIGN AND ANALYSIS

The clinical trial design depends on the objective(s) of the trial and the scientific question(s) to be answered. If the trial is conducted with a view to providing data for regulatory purposes, reference should be made to scientific guidelines for drug development in older patients, including EMA guidelines. In general it is preferable to include both non-geriatric and geriatric patients in the same study(ies), which can facilitate observation of age-related differences. In some cases a separate study in the geriatric population can be preferable.

An appropriate representation of the geriatric population, including patients with comorbidities and concomitant therapies should be enrolled in a clinical development programme to characterise the safety and efficacy of the drugs and allow application to everyday practice.

Clinical trials involving older people should reflect the importance of specific end-points such as quality of life, functional capacities, compression of morbidity and clinically relevant measures.

An appropriate comprehensive geriatric assessment could be used as criteria for randomization and for outcomes in designing clinical trials.

Research in the setting of palliative care will look at the complex quality of life issue in relation with the end-points for interventions where the older population QoL becomes more important than chronological length of survival, particularly in the frail very old...

To ensure the feasibility of clinical trials to be performed, it is recommended that the trial design be set up following consultation of the older patients to be involved in the trial, or with patient representatives. As is the case for trials in younger adults, all measures to avoid bias should be included in trials performed in the older population. For example, unblinded and/or uncontrolled trials for the demonstration of efficacy are subject to increased bias and should be avoided whenever possible.

Whenever possible (e.g., when differences in product mode of administration are impossible to mask), open trials should include provisions for blinding of assessment. Assessment, i.e., a systematic evaluation and documentation, in many cases will be based on the assessment by relatives or other carers, but in most circumstances the evaluation by the older patients themselves will be appropriate.

Trials without a control group for demonstration of efficacy should be avoided in principle. They have limited usefulness for the demonstration of safety, unless they are used prospectively for longitudinal studies or in predefined subgroups.

Alternative (less conventional) designs and/or analyses should be justified and it is recommended that they should be agreed with competent authorities when used with a view to provide data for regulatory purposes.

Modelling and simulation (M&S) methods can be used in place of clinical trials (CTs) in some cases (eg to generate appropriate data and avoid unnecessary use of older patients in CTs) and the use of such methods should be formalized in guidance.

The size of the trial conducted in the older patients should be large enough to demonstrate the appropriate efficacy with sufficient statistical power, recognizing the consideration of a higher dropout rate. In consideration of the analysis of risks and benefit, trials involving fewer older patients should be weighed against trials involving more patients but using less invasive

procedures. Adaptive, Bayesian or other designs may be used to minimise the size of the clinical trial.

4.2 GERIATRIC CONTROL GROUPS

The use of control groups, including the use of placebo and/or active comparator, should be based on equipoise¹ (32), should be appropriate to the condition(s) under investigation in the trial. It should be justified on scientific and ethical grounds, consistent with ICH GCP and the Declaration of Helsinki.

4.2.1 Use of comparator

Use of placebo in the older adults is more restricted than in younger adults, because some older patients cannot consent, and may not understand their use and purpose.

The use of placebos should only be allowed when it does not mean withholding effective treatment, particularly for serious and life threatening conditions. The use of a placebo is often needed for scientific reasons, including in geriatric trials. The use of a placebo may be warranted when evidence for any particular treatment is lacking or when the placebo effect is known to be very variable (e.g. pain). As the level of evidence in favour of an effective treatment increases, the ethical justification for placebo use decreases.

The use of a placebo is not equivalent to the absence of treatment, for example it could be used as well as standard care. In all cases, its use should be associated with measures to minimise exposure and avoid irreversible harm, especially in serious or rapidly evolving diseases. As appropriate, rescue² treatment and escape procedures³ should be set up. Other situations where the use of placebo should be scrutinised and challenged, include run-in periods where a protocol requires active treatment to be withheld.

Situations in which a placebo may be considered as a comparator, for example, might be when there is no commonly accepted therapy for the condition and the investigational medicinal product is the first one that may modify the course of the disease process, or when the commonly used therapy for the condition is of questionable efficacy or carries with it a high frequency of undesirable adverse reactions and the risks may be significantly greater than the benefits.

Other trial designs should be considered if appropriate. Active-control trials may be more difficult to interpret than placebo-controlled ones but may provide useful information on comparative benefit/risk balance. Therefore it is as important to discuss the exclusion of placebo, as it is to discuss its inclusion for geriatric clinical trials

4.2.2 Superiority versus non-inferiority trials

Equivalence and non-inferiority trials, and in particular the choice of equivalence or non-inferiority margins in relation to sample sizes feasible in the geriatric population, raise issues such as variability (add references), and should be fully justified when used instead of superiority trials. In addition, inconsistent trial conduct may further blur differences between treatments in equivalence or non-inferiority trials. Existing guidelines on methodology issues and/or specific EMA guidelines per therapeutic area should be consulted.

¹ also known as the **principle of equipoise**, provides the ethical basis for medical research that involves assigning patients to different treatment arms of a clinical trial. The term was first used by Benjamin Freedman in 1987.^[1]

² Rescue refers to treatment that may be given on top of trial medications to avoid danger or distress, for example pain treatment, as soon as the patient reaches a defined level.

³ Escape refers to prompt removal of subjects whose clinical status worsens or fails to improve to a defined level in a trial.

4.2.3 Comparative effectiveness research

The issue of comparative effectiveness study is also relevant to research in geriatric medicine and is being pursued at the European level (33).

4.3 PAIN, DISTRESS AND MINIMISATION OF FEAR

Physical, emotional and psychological distress should be prevented as much as possible, and effectively treated when unavoidable. This requires that physical pain and distress intensity is assessed and regularly monitored according to guidelines and appropriate validated scales, particularly in older patients who cannot express it. Effective treatment in relation to the intensity of pain should be administered and reviewed regularly on the basis of the assessments performed. In addition, if sedation is needed, monitoring should be set up and the appropriate level of sedation needed for the procedure(s) should be maintained.

Painful and invasive procedures should be minimised. Population approaches and sparse sampling for pharmacokinetic data may reduce the number of blood samples in older subjects.

Appropriate explanations should be given to the older research participant/patient prior to any investigation or procedure, in order to decrease anxiety and anticipation of pain, in honest, but not frightening terms. Any procedures that might also lead to embarrassment of the older patients (such as undressing) should be avoided or explained. In order to minimise pain, distress, and fear, facilities should be appropriate for older patients care, and the personnel should be trained to look after older patients and supervised by experienced health care professionals. Staff should be trained to communicate with legal representatives and with older patients. Older patients in a trial should be hosted in a familiar environment, including appropriate furniture, activities, where appropriate, and skilled personnel should address their concerns.

The variability of response to pain, distress and fear between older patients should be taken into consideration. Different reactions may be expected, when older people are affected by a chronic or acute disease.

4.4 RISK ASSESSMENT AND MONITORING

The interest of all patients should always prevail over that of science and society. This is paramount when assessing and monitoring risks. Risks are to be viewed in balance to the benefit (Annex 12).

Older people who are not able to consent should not be included in a research study that has no likelihood of benefit for them, unless this research cannot be performed instead with patients capable to consent, and the research results only in minimal risk and burden to promote the condition of the patient population represented by these older research participants. There may be circumstances where research may be performed on such patients provided that both the legal and or appropriate representative has given consent.

4.4.1 Assessment of risk

Risk assessment is a crucial step in evaluating a protocol and conducting the trial. Risk is defined as potential harm (real or theoretical) or potential consequence of an action. It may be physical, psychological, or social, and may be immediate or delayed. It may vary according to age groups. Risk should be assessed in terms of probability, magnitude and duration. Geriatric trials should be analysed for potential risks, including those that may

not usually be of concern in younger adults because medicines or procedures may cause adverse effects in older participants that have not been identified in young adults.

It is the responsibility of the investigator to make a thorough analysis of the risks in the trial and to describe this in the protocol so that research ethics committee may determine whether to provide a favourable opinion or not. Risks are not limited to physical harm; they may include psychological and relating to information (e.g. genetic diagnosis) risks. The unavailability of appropriate geriatric formulations may also incur risks. Disclosure of a risk for an incurable disease or violation of privacy may also cause potential harm.

Risk assessment includes the evaluation of the risk of the medicinal product tested or the control substance, the risk of withholding active treatment in some cases and the risk of the disease itself. Potential harm may include invasive procedures and the intrusiveness of research processes and demands, the severity and seriousness of potential harm, the reversibility of adverse effects and reactions, and their preventability. The accumulation of research projects in the same population (over-studied population) is another source of potential harm. Multiple clinical trials in an individual should be discouraged.

In the case of emerging issues during a trial with potential conflict between the older patient's interest and research interest, the protocol should envisage the management of such issues, e.g., harm in giving versus harm in withholding treatment. In addition to the risk inherent to the trial, there is a need for evaluation of external risks, for example linked to the centres involved with variable level of expertise and / or experience.

Risk assessment is difficult in practice as probabilities are unknown; the elements that influence the risks should be identified in the protocol. Finally, any identified risk should be associated to measures to prevent, minimise and monitor such risks as much as possible.

The participant must always be made aware of these arising conflicts and given the opportunity to withdraw.

The determination of the levels of risk and the associated potential benefits are the basis for ethical approvability. The following distinct risk levels are proposed as a means to decide on the ethical acceptability of trials:

- Minimal risk, which could be defined as probability of harm or discomfort not greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests
- Minor increase over minimal risk - Greater than minor increase over minimal risk.

4.4.2 Monitoring the level of risk

The level of risk may evolve over time, during the trial and with developing knowledge. It is important to evaluate also whether the risks differ by age e.g. impairment of renal function. Risk should be continuously monitored and pre-specified in the protocol. Rules about the stopping of the trial should be included in the protocol, especially for unscheduled or scheduled analyses in relation to safety or non-compliance.

Certain studies require the use of a Data and Safety Monitoring Board (DSMB), which should be consistent with regulatory guidance document. The DSMB should benefit from geriatric expertise.

In line with the Clinical Trials Directive, the sponsor of the clinical trial should identify and assess the risks (real and theoretical) and harm induced by the investigational medicinal products in the safety report submitted once a year throughout the clinical trial, or on request, to the competent authority and the relevant research ethics committee of the concerned Member States. In this report the sponsor should perform a specific analysis of the subjects' safety in the geriatric population enrolled in the clinical trial, and provide an

update of the benefit-risk evaluation for the geriatric population, in the light of scientific developments or events arising in the course of the research.

4.5 BENEFIT AND MEASURES OF BENEFIT

Direct benefit refers to benefit for the individual and / or benefit for the group. For the purpose of this document, the term “indirect benefit” is not used.

Benefit can be defined as progress in treatment, diagnosis, or prevention for the older subjects or the group of older patients affected. It is a tangible outcome that may be experienced by the subject. This may be obtained through either increased efficacy or safety resulting in a better benefit-risk balance, or through the provision of an alternative to existing treatment with at least similar expected benefit risk balance. Benefit can also be obtained through a contribution to patient care (for example, better route of administration, decreased frequency of dosing, improvement in relation to potential medication errors or compliance, reduced treatment duration, or a clinically relevant formulation).

Benefit for the group, i.e., older patients affected by the same disease, or a disease which shares similar features and for which the medicinal product may be of benefit, could be defined by increased knowledge of the condition and /or treatment, which would possibly result in better diagnosis, treatment or prevention. Measures of such benefit would include the importance of knowledge gained, severity of the issue to be addressed, whether the issue is common or not, the likelihood of obtaining results from the proposed research, and the usefulness of benefits obtained.

4.5.1 Balance of benefit and risk

The determination of the levels of risk and the associated benefits are the basis for ethical approval. The risk levels should be presented by the sponsor and assessed by the research ethics committee. As the assessment of the risk and the benefit may be based on probabilities and assumptions, respectively, this should also be balanced with the severity of the condition or diseases to be studied and the benefit and risk of alternative treatments. In the following examples, levels of risk are considered to be balance with the benefits for a trial with the geriatric population:

- Minimal risk with benefit for the individual or benefit for the group.
- Minor increase over minimal risk, with benefit to individual or benefit to the group, and with the benefit to risk balance being at least as favourable as that of available alternative approaches.
- Greater than minor increase over minimal risk with benefit for the individual that is especially favourable in relation to available alternative approaches for the individual's condition.

4.6 ASSAYS IN RELATION TO THE PHYSIOLOGICAL STATE OF THE OLDER PATIENT

Assays, investigations and blood sampling volumes related to the trial should be described and justified in the protocol.

The number and type of assays and investigations should take into consideration the physiological condition of any older patient to be included in the trial, especially their renal and hepatic function: appropriate facilities and material should be used. Alternative sampling (e.g. urine or saliva sampling) for pharmacokinetic studies should be preferred when possible. In principle, general and / or local anaesthesia should be used as appropriate for painful

and/or invasive procedures. Timing of sampling should be co-ordinated as far as possible to avoid repeat procedures and to avoid repeat sampling during the day in order to minimise pain and distress, and the risk of iatrogenic complications. Trained staff should perform sampling. The number of attempts for sampling should be limited. Timing of sampling and number of sampling attempts should be defined in the protocol. For example, it is recommended that after one unsuccessful attempt, another experienced person take over the procedure.

5. TRIALS WITH HEALTHY OLDER PARTICIPANTS

Many relatively healthy 70 year-olds and over take different medications and may therefore be excluded from healthy volunteer studies although they are representative of this population.

Some studies need to be performed in very old people when variability is very high, who are healthy at the time of the trial. Prevention trials or geriatric vaccine trials, including immunogenicity studies, will fall into this category but include the target population likely to benefit. Trials in older persons with intermittent diseases (e.g., flare-ups or seizures) are acceptable because even in the “healthy” phase older subjects are affected. Whenever possible the younger old people and less frail should be considered for inclusion before the older old or the frail.

6. INDIVIDUAL DATA PROTECTION

As in other patient populations, high standards of privacy, security and data protection, as well as respect for research participants’ rights, must be observed.

The confidentiality of medical records must be protected in accord with applicable laws including data protection laws.

Where personal information on older patients is collected, stored, accessed, used, or disposed of, the researcher should ensure that the privacy, confidentiality and cultural sensitivities of the subject and the community are respected. Older patients participating in a trial are entitled to know any information collected on their health. Other personal information collected for a research project can be made accessible to them if they so wish in conformity with national laws on the protection of individual data.

7. UNNECESSARY REPLICATION OF TRIALS

It is considered unethical to replicate unnecessarily trials in the older and very old patients. This can only be avoided by ensuring that information gained in any trial is made available to researchers and the public

7.1 PUBLICATION OF GERIATRIC TRIALS AND RESULTS

Registration of geriatric clinical trials and publication of results including unfavourable ones, together with a thorough analysis of the literature should allow detection of similar trials, with similar aims, and thus prevent unnecessary duplication of trials in the older patients.

7.2 INTERNATIONAL DATABASE AND AVAILABILITY TO THE PUBLIC

There is an ethical duty to check whether existing knowledge is available to modify the initial hypothesis for the trial. Public access to ongoing and completed trials through existing databases will facilitate avoiding replicating unnecessarily trials in older patients.

8. ADVERSE REACTIONS AND REPORTING

Rules and obligations for adverse reactions reporting in geriatric trials are identical to those in younger adults, in particular, but not exclusively, the notification of serious adverse reactions observed in clinical trials. The EU pharmacovigilance Regulation and its provisions should contribute to improving adverse events reporting through RMPs (Risk Management Plans) and PASS (Post Authorization Safety Studies).

As adult data are poorly predictive of safety in the older patients, reporting may cover target organs and types or severity of reactions differing from that expected in adults. A specific assessment of the adverse reactions associated with the administration of the investigational medicinal product in the older subjects should be performed in the annual safety report.

9. INSURANCE ISSUES

Insurance is mandatory according to the Clinical Trials Directive (Article 3(f)). Obtaining insurance for trials performed in older patients may be challenging, for example, because of different insurance regulations in Member States, Research ethics committees should pay careful attention to the insurance document.

10. TRIALS IN OLDER PATIENTS IN NON-EU COUNTRIES

According to Directive 2001/83/EC as amended by Directive 2004/27/EC, clinical trials submitted in a marketing authorisation application in the EU, which were performed in non-EU countries, should be conducted in accordance with the principles of Good Clinical Practice and the ethical requirements equivalent to the provisions of Clinical Trials Directive and should comply with good manufacturing practices of EU countries. These principles should also apply for geriatric trials where the medicinal product is not studied with a view to obtaining a marketing authorisation. The laws and regulations of the countries in which the trials are carried out should be respected.

Ethical standards should be no less exacting than they would be for research carried out in EU, countries and the trial documentation should be submitted for ethical and scientific review in the EU Member State in which the sponsor resides and in the host country.

The trial should ensure that it responds to the public health needs and priorities of the country in which it is carried out. It is the responsibility of all involved parties to ensure that this is respected and that the geriatric specificities, including assent are obtained for the older patients.

The recommendations in this document should be followed by EU researchers and sponsors, carrying out trials in third countries, as well as by ethics committees reviewing such trials or their results.

11. ETHICAL VIOLATIONS AND NON-COMPLIANCE WITH GOOD CLINICAL PRACTICE

GCP compliance of clinical trials is required. Although not specific to geriatric trials, ethical violations and non-compliance with GCP is particularly important, as some older people are a

vulnerable population. There is a role for research ethics committees and competent authorities in case of violation and non-compliance with GCP. Violations fall into critical, major and minor issues according to whether and to which extent patient safety and scientific value are compromised. The preferred option to avoid such violations is education, training and counselling. Research ethics committees should liaise with competent authorities if they are informed of such violation or non-compliance.

Compliance with GCP should be explicit in publications, and results of studies conducted unethically should be made public with a clear warning specifying the unethical aspects. Information on such trials is needed to avoid unnecessary repetition of the trials and to protect future trial participants. If non GCP-compliant data are submitted as part of a marketing authorisation application, the quality of the data, the study results, and consequently the validity of the marketing authorisation application should be scrutinised. Sensitivity analysis should be performed within the GCP-compliant full data set, and in some cases also in comparison with all GCP-non-compliant data. The overall reliability of the trial should be questioned. Subsequent measures (including initial review) should be taken in accordance with national legislation, if appropriate.

12. ANNEX 1: LIST OF ISSUES FOR A TRIAL WITH THE GERIATRIC POPULATION

List of issues to be taken into consideration for planning a geriatric trial:

1. Identification and scientific validity of the study question to be answered
2. Justification of the study to be performed in the older people
3. Evidence of direct benefit for the older subjects, or benefit for the group
4. The competence of the responsible study investigator and his/her team
5. The infrastructure of the institution or primary care practice that should be qualified and experienced in geriatric research in general and in particular in the field of the applied project.
6. The pre-clinical safety and efficacy data (investigator's brochure, available literature) that are preconditions for a geriatric clinical trial
7. The clinical results of adult studies (literature, investigator's brochure), if any.
8. Type and phase of the study
9. Use of placebo or active control
10. Appropriate formulations of medicinal products
11. Appropriate scales or measures of end-points (e.g., pain scale)
12. Study design and biometric planning in relation to the trial question
13. Design feasibility and information sheets checked with older/ patient representatives
14. Inclusion and exclusion criteria
15. Statistical methods
16. Criteria for the termination of the study
17. Safety measures including the set-up of a Data Safety and Monitoring Board (DSMB)
18. Appropriate pharmacovigilance procedures are put in place by the sponsor.
19. Study risks, pain, fear and discomfort
20. The potential risks (real and theoretical) have been weighed against the expected benefits for the older person enrolled in the clinical trial. The balance of expected benefit versus risks should be positive for the clinical trial.
21. Comprehensive, understandable Informed Consent and Information sheets for legal representatives
22. Understandable age specific Informed Assent and Information sheet
23. Anonymity of the data, as well as confidentiality of personal information related to the older subjects involved in the research, and to his/her family

24. Insurance of older participants, in the relevant country
25. If available, opinions of other ethics committees for international multicentre studies
26. Publication of trial results
27. Continuation of trial medication where appropriate

13. ANNEX 2: INFORMATION FOR INFORMED CONSENT

Information sheets should be separate for older patients/participants (and their legal representatives if necessary) whenever a protocol is specifically geared to the involvement of such patients: they should be concise in content, precise in language (e.g., use of non-technical terms), and appropriate for the older patients/participants (e.g., avoid abstract concepts, multiple options). The number of variations of information sheets should be kept to a minimum required to include substantially different wording or presentation. In addition, information sheets should not cause unnecessary distress. They should possibly be designed with participants, affected older patients. Information sheets should be harmonised throughout sites in multi-centre trials, and address similar age groups in multinational trials.

List of items recommended to be covered in the information sheets:

1. What is the purpose of the trial?
2. Why have I been chosen?
3. Do I have to take part?
4. What will happen to me if I take part?
5. What are the compensations?
6. What will I have to do?
7. What is the medicine that is being tested?
8. What are the alternatives for diagnosis or treatment?
9. What are the possible disadvantages and risks of taking part?
10. What are the side effects of any treatment received when taking part?
11. Is ionising radiation to be received, and which regulations are respected?
12. What are the possible benefits of taking part?
13. What happens when the research study stops?
14. What if there is a problem?
15. Will my taking part in the trial be kept confidential?
16. What will happen if I don't want to carry on with the trial?
17. What are the options if I stop taking part in the trial?
18. How is my General Practitioner/Family doctor involved?
19. What will happen to any samples taken from my body?
20. Will any genetic tests be done?
21. What will happen to the results of the research trial?
22. Who is organising and funding the research?
23. Who has reviewed the trial and what are the results?
24. Contact details for information or complaints

14. ANNEX 3: EXAMPLES FOR LEVELS OF RISKS

The following table provides examples of risk evaluation of measures carried out for the purpose of a trial. For example, an existing central venous line may reduce the pain and invasiveness of blood sampling, but also increases the risk of infection and of excess blood losses with line handling.

The risk evaluation of some of the measures (including, but not limited to those marked *) is very much dependent on such circumstances and on the context of its use in the trial. In addition, the risk level increases with the increase in frequency of the measures and with the susceptibility to harm of involved/exposed organs. The categorisation proposed in the table applies to single or very infrequent use of the measure. The examples presuppose that the measures are carried out to the highest professional standards.

15. REFERENCES

<i>No or minimal risk</i>	<i>Minor increase over minimal risk</i>	<i>Greater than minor increase over minimal risk</i>
History taking Clinical examination Behavioural testing Psychological testing* Quality of Life assessment	Venipuncture* Finger prick* Subcutaneous injection Breath condensate collection Collection of saliva or sputum Collection of hair sample Collection of tissue removed from body as part of medical treatment* Topical analgesia* Stool tests Bio-impedancemetry Transcutaneous oxygen saturation monitoring (pulse oxymetry)* Blood pressure monitoring Electroencephalography Electrocardiography Vision or hearing testing Ophthalmoscopy Tympanometry Lung function tests (peak flow, exhaled NO, spirometry) Oral glucose tolerance test Ultrasound scan Digitally amplified chest or limb X-ray* Stable isotope examination Arterial puncture PH metry Nasogastric tube insertion and use Transcutaneous oxygen or carbondioxide tension monitoring Electrophysiological measurements (using stimulation) Exercise testing (ergometry, spiroergometry) Pulmonary function testing Peripheral venous lines Polysomnography Fasting (≥ 1 meal)	Urine collection with bag Urine collection via endoluminal or suprapubic catheter Spinal CSF tap Bone marrow aspiration MRI scan X-ray other than digitally amplified chest or limb X-ray CT scan* X-ray DEXA bone density measurement Use of contrast media Paracentesis Skin punch biopsy Airways or skin hyperactivity challenge test Heart catheterisation Endoscopy Biopsy Surgery or modification of standard surgical procedure carried out as part of medical treatment Sedation Anaesthesia Systemic analgesia Hypoglycaemia test Unstable isotope usage PET scanning

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22. Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (revision 2) as required by Article 18 of Directive 2001/20/EC.
23. Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use (revision 1) as required by Article 8 of Directive 2001/20/EC.Feb. 2006: 1-34.
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