

Ethical issues in endoscopy: patient satisfaction, safety in elderly patients, palliation, and relations with industry

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Authors

S. D. Ladas, B. Novis, K. Triantafyllou, R. Schoefl, T. Rokkas, C. Stanciu, P. Isaacs, S. N. Willich, O. Ronn, H. Dremel, G. Livadas, B. J. Egan, S. Boyacioglu, A. Selimovic, R. Pulanic, J. A. Karagiannis, J. P. Van Vooren, E. Kouroumalis, C. O'Morain, A. Nowak, J. Deviere, P. Malfertheiner, A. Axon

Institutions

European Society of Gastroenterology, Munich, Germany

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Corresponding author

S. D. Ladas, MD

Hepato-Gastroenterology Unit
"Attikon" University General
Hospital
Medical School,
Athens University
1 Rimini Street
124 62 Haidari
Greece
Fax: +30-210-5326422
sdladas@hol.gr

Introduction

The explosive development of gastroenterology and gastrointestinal endoscopy over the past few years, with clinical trials of powerful new drugs and top-quality endoscopes and accessories, has led to a huge increase in the diagnostic and therapeutic potential of modern gastroenterology. At the same time the percentage of elderly people in Europe has increased, patients attending gastrointestinal endoscopy units are expecting to undergo painless endoscopy procedures, and palliative endoscopic therapy is increasingly being used for patients with lethal gastrointestinal diseases. This new environment presents a number of ethical issues and necessitates an updated consensus applicable in the clinical practice of gastroenterology.

The European Society of Gastrointestinal Endoscopy (ESGE) and the Organisation Mondiale d'Endoscopie Digestive (OMED), in collaboration with the United European Gastroenterology Federation (UEGF), organized the Second European Symposium on Ethics in Gastroenterology and Digestive Endoscopy on the island of Kos, Greece, in July 2006. Twenty-three expert gastroenterologists, surgeons, and scientists from the biomedical industry participated in four workshops, aiming to formulate a consensus statement after presentation of the topics, discussion, and voting in a plenary session. We are happy to present these consensus reports here in *Endoscopy* and hope that they will help our colleagues in their clinical practice.

Workshop 1: Patient satisfaction with endoscopy

B. Novis (*Rapporteur*), C. Stanciu (*Moderator*), S. D. Ladas, S. Boyacioglu, A. Selimovic, R. Pulanic, J. A. Karagiannis

Introduction

Patient satisfaction is an important issue in achieving excellence in health care. Numerous attempts to define patient satisfaction have been made. An acceptable definition is that of Maciejewski et al. [1] who suggest that it represents a patient's cognitive or emotional evaluation of a health-care provider's performance and is based on relevant aspects of a patient's experiences and perceptions. Yacavone et al. [2] from the Mayo Clinic in Rochester suggested seven possible domains of satisfaction with endoscopy: (i) the technical quality of care, including the skills of the endoscopist; (ii) the comfort and tolerability of the procedure; (iii) the "art" of care (the personal manner of the endoscopy staff); (iv) the provision of an adequate explanation of the procedure; (v) communication with the physicians before and after the procedure; (vi) the endoscopy suite environment; and (vii) waiting time or delays.

Factors that affect patients' tolerance of endoscopy

Several factors influence patients' tolerance of gastroscopy, the most important being anxiety [3]. Anxiety can result in a more difficult and painful procedure. Relieving anxiety before gastroscopy using various educational and explanatory materials [4], relaxation and coping techniques, and the use of thinner endoscopes have all been suggested for patients who are undergoing unsedated endoscopy [5]. An assessment of patient tolerance has indicated that people over the age of 50 years and men are more tolerant

[6], as are those with prior experience of endoscopy. Women, younger patients, people with pharyngeal sensitivity, and those who are undergoing their first procedure experience more anxiety.

The use of conscious sedation varies in European countries, but it is used less frequently in Europe than it is in the United States [7]. However, in a study reported by Abrahams et al. [6], only 61% rated the comfort of the procedure without sedation as "acceptable." Therefore, in certain patients (i.e. those who are expected to have a high degree of anxiety) conscious sedation is indicated and will result in higher degrees of patient satisfaction. Triage of patients by factors influencing tolerance might be useful.

Most colonoscopies are associated with little or no pain and are easy or only mildly difficult to perform. In experienced hands, colonoscopy without sedation has a high cecal intubation rate, similar to that of sedated colonoscopy [8]. However, it is often difficult to predict how difficult or painful the examination will be [9]. In some countries colonoscopy is traditionally performed with conscious sedation, the advantages including better acceptance and tolerance because sedation blunts the sensation of intraprocedural pain and induces retrograde amnesia for painful stimuli.

Factors favoring sedated colonoscopy are a high degree of anxiety, younger age (< 50 years), female sex (particularly women with irritable bowel syndrome), gynecological disease, and a history or previous hysterectomy or other pelvic surgery. The main factors that favor unsedated colonoscopy are male sex, previous segmental colonic resection, and prior good experience with colonoscopy.

Preprocedural educational interventions and psychological preparation can benefit some patients. It might be possible to target patients who are likely to be intolerant of the procedure to arrange an alternative method of deep sedation, i.e. with propofol.

Conscious sedation and patient satisfaction with endoscopy

The question of whether sedation and analgesia improve satisfaction with endoscopy is debatable. Overall, evidence favors sedation as it results in a higher degree of satisfaction, both for patients and physicians. The common sedatives used, such as midazolam and diazepam, and the analgesics pethidine and fentanyl are generally safe but do require careful monitoring of oxygen saturation and pulse rate, as hypoxemia and hypotension are the main complications observed. Oversedation can induce respiratory depression and delay recovery in elderly patients and in patients with cardiopulmonary problems. This has led to the targeting of groups of patients in whom endoscopy without sedation is possible, as discussed previously.

On the other hand, propofol induces deep sedation and this is a major advantage for painless colonoscopy in selected patients. In most countries propofol can only be administered by anesthetists; in other countries, staff trained in the use of propofol, who are able to perform tracheal intubations, and who are not involved in the procedure may administer propofol.

Assessment of patient satisfaction with endoscopy

The pre- and postprocedural factors that influence patient satisfaction have not been investigated to any great extent so far and very few data are available on this topic. Reliable methodology to assess these factors is lacking. A modified Group Health Association of America-9 survey (mGHAA-9) [10] was further modi-

fied by the American Society for Gastrointestinal Endoscopy, resulting in a 15-item questionnaire developed by Yacavone et al. [2] that aimed to rank aspects of satisfaction with endoscopy practice. These aspects include:

- ▶ Access-related factors
- ▶ Appointment-related factors, such as the waiting time for an appointment (rated low, with a score of 12), the explanation given for the delay (rated low, score 13)
- ▶ Information-related factors, including the explanation of the procedure (medium-rated, scoring 6) and adequate answering of questions (middle rating, score 7)
- ▶ Procedure-related factors, including the endoscopist's technical skill (rated high, score 1), the endoscopist's personal manner (rated high, score 4), the personal manner of staff (with a medium-to-high score of 5), adequate control of discomfort caused by the procedure (rated medium to high, with a score of 5), the appearance of the endoscopy suite (rated low at score 9), noise level (rated low, scoring 13), and the degree of privacy (rated low, scoring 11)
- ▶ Discharge-related factors, such as postprocedure advice (rated low, with a score of 7)

A crucial question is how to measure patient satisfaction with endoscopy. Should this be done using written questionnaires, by personal interview or by email? When should this be done? Immediately after endoscopy, or 3–6 months later? What type of questions should be included in a questionnaire? Open-ended questions which enable the patient to make comments can lead to more meaningful results than closed questions. Written surveys tend to be the most cost-effective as well as the most reliable method. The survey should be short, specific, and easy to understand [11]. The drawing up of pilot questionnaires, with patients helping to decide on the wording and design of the questionnaire itself is recommended. [12]. Choice of wording is important, so as not to influence the patient's rating of satisfaction with the endoscopic procedure [13].

Consensus statements accepted by voting

- ▶ Factors that should be modified in order to improve patient satisfaction with endoscopy include: the ease of access to endoscopy, shortening of appointment waiting time, minimal procedural discomfort, prompt consultation with the patient after the procedure, and the personal manner of the endoscopist and the supporting staff.
- ▶ An annual assessment of patient satisfaction should be made using a written survey dealing with various access issues, patient–physician and personal staff issues, and quality issues:
 - Questions should be short, specific, and easy to understand. Always include general questions as well, such as "Overall, how satisfied were you?"
 - Questions should be answered using a five-point scale from poor (score 1) to excellent (score 5).
 - One or two open-ended questions should be included.
 - A minimum of 200 responses is required to be able to draw significant conclusions. As the expected response rate is about 33%, at least 600 questionnaires should be distributed.
 - Mailed surveys are preferred over personal-distribution or email surveys.
 - Inclusion of demographic data in the survey should be very useful.
 - In general, the questionnaire should be anonymous.

- A pan-European endoscopy satisfaction survey should be conducted, based on these indicators, in order to establish a framework for the establishment of a European endoscopy procedure standard.

Workshop 2: Safety of endoscopy in the elderly

▼
K. Triantafyllou, P. Isaacs (*Rapporteurs*), S. D. Ladas (*Moderator*), A. Nowak, E. Kouroumalis

Introduction

The population is rapidly aging. In 2000, 12.6% of the total population were elderly (aged 65 years or over) and this proportion will continue to rise over the next decades [14]. Aging is associated with an increased incidence of gastrointestinal disorders such as cancer, reflux, ischemia, and biliary tract diseases, which co-present with age-related disorders such as cardiovascular and pulmonary dysfunction, as well as variation in responses to medications [15, 16]. The rate of hospitalization due to complications of cholelithiasis (e.g. acute cholecystitis) has doubled in the elderly over the past 30 years for example [17]. Moreover, the use of gastrointestinal endoscopy in geriatric patients is growing due to the extended application of technology to the clinical problems of this age group [18].

Ethical issues surrounding the use of diagnostic and therapeutic endoscopy in this age group are related to limited life expectancy and the complexity of health problems in the elderly. There can be considerable difficulties in obtaining informed consent, and standard sedation and analgesia can expose this fragile population to major risks. It might be appropriate to continue screening for colorectal neoplasia in the elderly as long as there are no life-limiting co-morbidities, and high-risk endoscopic procedures represent a true alternative to surgery only if there is evidence for benefit in an elderly patient.

Informed consent – should a relative also sign the form?

Obtaining informed consent prior to an endoscopic intervention can be complicated in the elderly. The treating physician and the endoscopist should assess the patient's cognitive function and address barriers to communication (impaired hearing, vision, and literacy) before discussing intervention or treatment, preferably with the relatives present [19]. Truthful verbal and written information should be provided early on, to allow the patient to discuss this with their relatives and the medical staff. Ideally, the information should be based on local outcome data concerning their age group.

The Mental Capacity Act 2005, which comes into force in April 2007 in England and Wales, not only provides an ethical approach but also sets out clear legal requirements for assessing competence and for treating incompetent patients. The Act requires that the views of family members on what is in the patient's best interests should be taken into account, but they have no legal power to consent on behalf of their incompetent relative [20]. However, the situation is not the same in all ESGE-related countries. In Israel, there is a requirement for a legally nominated family member or a Justice of the Peace to give consent on behalf of the incompetent patient, while in countries like Greece, Poland, and Slovenia it is common practice for relatives to give written approval before any medical procedure.

The panel felt that the statement of the previous Symposium on Ethics [4] is still valid: "According to the International Ethics

Code, the physician cannot give treatment to a mentally impaired patient without the agreement of a close (first-degree) relative. In an emergency or where there are no relatives, the physician takes responsibility to do his best in the interest of the patient." However, at the presentation during the general assembly the majority agreed (by vote) that when mentally impaired elderly patients require endoscopy, discussion with the closest available relative is strongly advised. However, it is not advisable to have the relative sign an agreement, because the overall responsibility rests with the physician.

Safe sedation for the elderly

The use of sedation/analgesia in gastrointestinal endoscopy varies between European countries [7]. Unfortunately, sedation is not risk-free and there are a variety of physiologic processes that increase the risk of sedation in the elderly [21]. Age-related disorders and excessive or rapid sedation contribute to complications such as cardiovascular and pulmonary dysfunction [21]. The risks of sedation and alternatives to sedation should be discussed during the informed consent procedure [22], and particular risks should be assessed before the procedure by the treating physician or the endoscopist.

Data show that elderly patients tolerate unsedated diagnostic endoscopy better than younger patients [23, 24]. The general assembly decided that, although this would not be an attractive option in many parts of the world, it is of ethical value to give to a well-informed, relaxed elderly patient the opportunity to have an endoscopic procedure performed without sedation/analgesia or with sedation available on demand. However, if sedation is needed, guidelines recommending the use of less sedation at a lower dose (usually half the normal adult dose) and at a slower rate [25, 26] must always be adhered to. Midazolam, pethidine, meperidine, and propofol are the most commonly used sedatives/analgesics. These have all been shown to be safe when used in the elderly, in low doses and with careful titration [16]. Everyone who administers sedation during endoscopy should have had training in the pharmacology of the various agents used and in airway management [27]. Similarly, qualified personnel should monitor the sedated elderly patient. Although standard monitoring is advised [26], it is ethically recommended that blood pressure and oxygen saturation should be monitored intensively, and oxygen supplementation must be used liberally.

Screening for premalignant lesions

Screening for premalignant lesions is controversial and is not well documented in the elderly. Fundamental questions that should be answered are: "Is screening really necessary?" and "When to stop?" [28]. Financial factors, social attitudes, and moral considerations are implicated when trying to find clear answers to these questions, but it is debatable whether age should be considered a decisive factor. One should consider first the cost-effectiveness of the proposed screening program, but, most importantly, the expected impact (if any) on life expectancy should be taken into account. It should be stressed that all data and recommendations for the elderly are based on Markov models and that no actual clinical trials have validated these models.

A number of different screening schedules have been proposed for patients with Barrett's esophagus. However for the elderly, all Markov models run for either 30 years or up to the age of 75. It is highly likely therefore that over this age no effect on life expectancy should be expected [29] and therefore no screening or

surveillance is justified in the elderly. Many recent investigations have agreed that colorectal cancer screening reduces the mortality from this neoplasm. However, things are not so clear-cut in the elderly. Screening is unlikely to show any survival benefit when the life expectancy is less than 5 years [30]. It is reported that colorectal cancer screening results in a gain in life expectancy of only 0.13 years for those aged over 80 years, compared to 0.85 years for people aged 50–55 years [31] and that the number of days of life lost after stopping screening at the age of 75 is only 9; at the age of 80 this figure is only 5 days [32]. Most investigators agree that screening is not necessary after the age of 80 years and that it is better to consider each case on an individual basis [33].

Apart from mathematical calculations, there are moral considerations to be taken into account. Should a doctor deny a patient even a limited increase in life expectancy? In fact, this might be equivalent to passive euthanasia. A lesson from the past should always be kept in mind: “I will use my knowledge only for the benefit of the patient, to the best of my judgment...” (from the Hippocratic Oath, 450 BC). There is no mention of age in this sentence! It is therefore ethically valid that if one is convinced that screening is helpful, then it should be applied to everybody, unless there is some contraindication.

High-risk therapeutic endoscopic procedures vs. surgery in the elderly

Only nonabdominal surgery in the elderly has a mortality rate similar to that of younger patients [34] and therefore endoscopic procedures, if applicable, are usually favored. Mortality of procedures is usually the main consideration but other major risks such as delirium and depression [35] are not taken into consideration often enough. The elderly perspective on life is one in which loss of social contact during hospitalization is as great a threat as physical morbidity.

The risk of an intervention can be reduced by addressing treatable medical conditions preoperatively. Treatment options should be discussed with the elderly patient (if he or she is competent), preferably with the relatives present, and the information on which a decision is to be based should ideally be local outcome data concerning their age group. This is sometimes difficult because elderly patients are usually excluded from trials that compare therapeutic endoscopy and surgery, meaning that solid data are not available.

Modern surgery can lead to excellent results in the elderly. For example, although laparoscopic cholecystectomy in elderly patients has a higher rate of conversion to an open procedure than occurs in younger patients, Pessaux et al. [36] achieved similar mortality (2%) and length of hospital stay in older patients when compared with under-65 s. When considering the management of common bile duct stones the era of laparoscopic exploration of the common bile duct is now firmly established and decisions regarding endoscopic retrograde cholangiopancreatography and sphincterotomy prior to cholecystectomy for these patients should depend on local experience.

On the other hand, therapeutic gastrointestinal endoscopy in the elderly is not trouble-free. These procedures can cause complications, some of them potentially lethal and probably often unrecognized as being complications of the endoscopy. The advice offered on any intervention should therefore be based on published evidence relevant to elderly patients, on local experience, and on the availability of techniques. Treatment plans should be recommended on the basis of fitness rather than age. Careful

pretreatment assessment and optimization of the elderly patient's condition is essential and outcome data specific to the frail elderly group are needed.

Consensus statements accepted by voting

- ▶ When mentally impaired elderly patients require endoscopy, discussion with the closest available relative is strongly advised, but it is not advisable to have them sign an agreement, the overall responsibility resting with the physician.
- ▶ Elderly patients tolerate unsedated diagnostic endoscopy better than younger patients. All sedatives, including midazolam, pethidine, meperidine, and propofol, have been shown to be safe in the elderly in low doses and with careful titration, and should be used when indicated. It is ethically recommended to intensively monitor blood pressure and oxygen saturation, and oxygen supplementation must be used liberally in the elderly.
- ▶ Screening is not necessary after the age of 80 years, but it is better to make decisions regarding each patient on an individual basis.
- ▶ Endoscopic intervention should be based on published evidence that is relevant to elderly patients. Treatment plans should be recommended on the basis of fitness rather than age. Careful pretreatment assessment and optimization of the patient's general condition are essential in the elderly.

Workshop 3: Palliative endoscopy – what does it change?



R. Schoefl (*Rapporteur*), J. Devière (*Moderator*), A. Axon, J. P. Van Vooren

Introduction

“Thinking in terms of continuous care must not mask the fact that there are break-off points in the history of an illness. Physicians must not entertain misleading illusions about pushing back death indefinitely or going as far as accepting death. It is possible to go beyond the normative patterns and to help patients to live with their serious illness, whatever the stage of the disease.” (J. C. Fondras [37])

Palliative endoscopy represents a small part of the wide spectrum of interventions, drug therapies, and psychological, religious, and social aids to maintain quality of life and preserve self-determination and self-esteem towards the end of life. Endoscopic palliation has been widely applied in biliopancreatic and esophagocardial malignancies for some years. Recently, obstructions of the small bowel and the large bowel have become new therapeutic targets. The target of palliation is to re-establish bile flow and food transit, thus addressing essential aspects of the quality of life.

Survival and quality of life after endoscopic palliation

Endoscopic palliation in malignant bile duct obstruction aims to prevent or treat cholangitis, relieve itching, improve nutritional status, and improve overall quality of life. A substantial amount of retrospective and prospective data shows that not only physical, but mental and social functions are improved by biliary stenting, which can eventually be combined with duodenal stenting and neurolysis. Randomized controlled trials have been published comparing the following treatment options:

- ▶ Stenting vs. surgical bypass: success and mortality were shown to be equal, with immediate complications more common after surgery, and recurrence of jaundice more common after stenting [38].
- ▶ Endoscopic stenting vs. percutaneous stenting: morbidity and mortality were shown to be lower after endoscopic stenting [39].
- ▶ Metal stenting vs. plastic stenting: metal stents were found to remain patent for longer than plastic stents [40].
- ▶ Duodenal stenting vs. bypass surgery: these have shown equal success, but stents allowed earlier feeding and a shorter hospital stay [41].

No definitive advantage could be found for preoperative stenting of patients with malignant jaundice before curative surgery. Some questions remain unanswered: it is still unclear whether hilar obstructions need bilateral drainage or do as well with unilateral stenting; and it is unclear how to identify which patients with obstructing liver metastases will gain a significant advantage from drainage procedures. The treatment of obstructed metal stents remains controversial and combinations of endoscopic methods with radiotherapy or chemotherapy and photodynamic therapy have not yet been studied sufficiently. To date, guidelines have not dared to state when palliative interventional techniques should cease and who should make that decision.

In esophagocardial malignancies the therapeutic target of palliative therapy is the restoration of swallowing, thus improving nutrition and preventing aspiration. Randomized controlled trials have compared self-expanding metal and plastic stents with rigid plastic tubes, and have demonstrated that self-expanding stents are associated with fewer complications and shorter hospital stay, but higher costs. Their superiority in relieving malignant obstruction is beyond doubt [42], but it remains unknown whether stenting and radiotherapy and chemotherapy are alternative, combined, or sequential treatment methods. The recent development of removable stents might favor a combined therapy of stenting first and chemoradiotherapy afterwards. A comparison of stenting and percutaneous endoscopic gastrostomy combined with best supportive care is still pending.

In summary, endoscopic palliative techniques are well defined with regard to their efficacy and their impact on quality of life. Options for retreatment are less well studied in these terms. Decisions on which palliative treatment or treatments to use in the elderly patient are probably best reached using an interdisciplinary team approach.

The limits of endoscopic palliation – when to stop?

Ethical questions concerning termination of treatment and the responsibility for this decision remain unsolved. Decision makers should keep in mind that the aim of palliation is mainly to relieve physical, psychological, and social distress. Normalization of laboratory tests or improvement in imaging studies is not a useful target for therapy. Symptoms such as anorexia, fatigue, and depression are particularly difficult to treat. The limits of treatment derive from the autonomy of the patient, legal considerations, and the personal preferences of the patient. Overall life expectancy, anatomical limits, risks, and costs further influence the process of decision making. Decisions should always be made together with the patient after sufficient information has been provided. During this process all the different choices of palliative therapies can be explained to the patient and the patient is then put in the position of the decision maker or the doctor in charge might have a clear preference which is proposed to

the patient. The choice of a priority treatment is easier when sufficient evidence, preferably from randomized controlled trials, is available. Nevertheless, the decision must be adapted to the particular needs of the individual patient [43].

An interesting discussion developed concerning the value of concentrating endoscopic palliative therapies in high-volume centers and whether systematic distribution into small-volume departments might be better. The relationship between competency and volume of procedures not only concerns centers as a whole but also individual endoscopists. High-level competency in palliative endoscopy should be integrated within multidisciplinary teams.

Organization of patient management and support

The concept of specialized palliative care has emerged only during the last 50 years (● Figure 1), this type of care emerging as the counterpart of curative care when the latter is no longer suitable (● Figure 2). Frequent transfers between these two “competing” types of care during the period of transition led to difficulties, however. In recent years, the concept of palliative care sited exclusively in dedicated departments has changed to a concept of permanent supportive treatment running in parallel with curative treatment (● Figure 3). The patient remains in the acute care unit as long as possible, assisted by specialists in palliative care. Only in the very last phase do patients move to a dedicated palliative unit, if that is necessary. Practical targets of improved palliative or supportive care include: more and better communication between all parties, the provision of more information for the patient, the use of a multidisciplinary palliative care team, and the provision of clear recommendations for home care. These goals will only be reached when palliative medicine becomes an integrated part of medical education and postgraduate teaching [44].

The concept of palliative care is often associated with euthanasia. Euthanasia, defined as medical assistance in dying for mentally competent, terminally ill patients who are suffering unbearably, is a criminal offense in most countries, but the hidden incidence is said to be high. Although a high proportion of people in Europe would not object to the law being broken in certain cases, the experiences of assisted suicide (which must be differentiated from euthanasia as defined above) reported by relatives reveal excessive guilt and a high rate of their own suicide. The subsequent discussion on the pros and cons of euthanasia was highly controversial. The attitudes of endoscopists throughout Europe were surprisingly different, as were the national laws in various countries. The arguments for and against euthanasia focused on the fear that the relationship between patients and doctors as well as relationships within families could suffer. For the patient, economic and ethical constraints might influence the acceptance of euthanasia. Patient autonomy was also discussed.

Consensus statements accepted by voting

- ▶ A multidisciplinary approach, regarding each patient on an individual basis, is highly recommended in palliative care.
- ▶ The choice of palliative endoscopic therapy should be made on the basis of all the scientific information available (i.e. an evidence-based approach).
- ▶ The combination of different palliative therapies and retreatment have been less well studied in terms of clinical efficacy and quality of life.

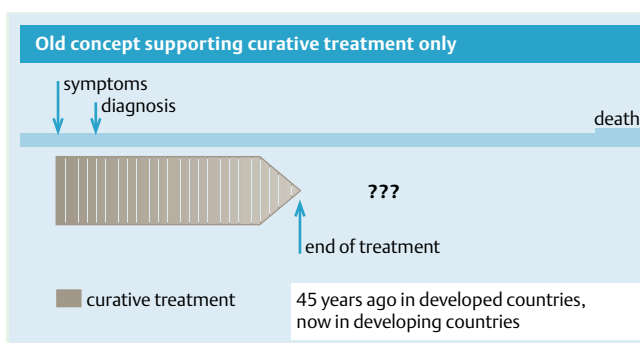


Figure 1 The old concept of curative care only, without palliative care.

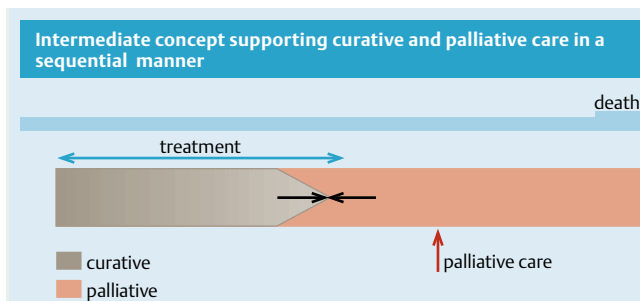


Figure 2 The intermediate concept of a dual approach, with both curative and palliative care, but with these delivered sequentially.

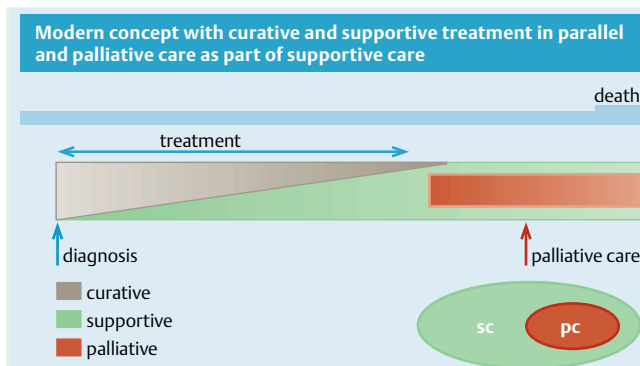


Figure 3 The modern concept of integrated supportive care (sc, supportive care; pc, palliative care).

- ▶ Ethical questions regarding “When to stop?” or “Who should decide?” are partially unresolved.
- ▶ Palliative endoscopic therapy is unethical when performed without proper training or experience or in a center without a suitable caseload or equipment.
- ▶ Recommendations to the patient should clearly stress the preferred choice of the responsible doctor when scientific evidence is available, but should be more open when evidence is lacking.
- ▶ Supportive care provided in parallel with curative treatment in acute care units, followed by care in palliative units only toward the end of life, reduces the need for palliative care units and avoids stressful transfers for the patient.
- ▶ Education in palliative care should be an integral part of teaching in medical schools as well as in postgraduate programs.

Workshop 4: Ethics in collaborative trials with industry

T. Rokkas (*Rapporteur*), P. Malfertheiner (*Moderator*), C. O'Morain, S. N. Willich, O. Rönn, H. Dremel, G. Livadas, B. J. Egan

Ethical concerns from the investigators' viewpoint

The Declaration of Geneva binds the physician with the words, “The health of my patient will be my first consideration,” while “[the] primary purpose of medical research...is to improve prophylactic, diagnostic, and therapeutic procedures and the understanding of the etiology and pathogenesis of disease.” [45]. In essence, the goal of the physician is to provide benefit to the individual patient, while the goal of a research investigator is to provide new knowledge that can help future patients. This in itself can represent a conflict for a physician as an investigator, especially in clinical trials in which uniformity between groups is important and alteration of treatment might be allowed only according to a rigid schedule rather than on an individual basis. Of course a major ethical concern in clinical trials with industry is finance. Of 11 meta-analyses, nine reported that industry-sponsored trials were significantly more likely to yield pro-industry results: the odds ratio of having industry sponsorship and pro-industry conclusions was found to be 3.60 (95% confidence interval 2.63–4.91) [46].

In a survey of published randomized controlled trials, the authors who disclosed a financial involvement acknowledged the following reasons for their financial interest: employment (30%), consultancies and honoraria (22%), grants (18%), educational/speaker's bureau (7%), stock ownership (7%), advisory board membership (5%), and patents/licenses (1%) [47]. However, despite the obvious ethical issue of an investigator receiving funding from industry, causing a bias in the study, there is evidence to suggest that industry-funded research is better [48]. Industry sponsorship appears to influence study outcome. A systematic review that included 37 studies investigated the relationship between sponsorship and study outcome, as well as the process for disclosure, review, and management of conflicts of interest: in the majority of studies the conclusion favored the sponsor [46]. Another systematic review included 324 cardiovascular medicine trials published between 2000 and 2005 in high-ranked journals and this revealed an association between funding source and the outcome of the study, favoring novel treatments over standard treatments [49]: overall, 67% of for-profit trials favored newer treatments over standard care, compared with only 49% of not-for-profit-sponsored trials. A similar relationship was observed for drug and device treatments. These results raise issues of differing underlying cultures of research in academia and industry. Academia has traditionally been characterized by the mission to educate and discover, driven by intellectual curiosity (“pure” motives). In contrast, industry is typically characterized by missions of translational research, commercialization, and profit making.

Over recent years, however, there appears to be a more mutual approach developing between the two cultures. The potential advantages are obvious, because translational research can be facilitated, interdisciplinary opportunities are enhanced, and there is more discretionary money for academic programs, professorships, scholarships, and fellowships, with cross-culturalization between the academic and industrial communities. On the other hand, there are important caveats, such as potential conflict of interest and commitment, possible loss of public trust,

expansion of federal regulations, conflict of academic interest, or even potential loss of freedom of academic exchange.

In this context, a methodological aspect of study design is of particular relevance. Randomized controlled trials have become the most important study type for the approval processes of new medical therapies, including drugs. Since its introduction in the 1950s the randomized controlled trial has developed into the “gold standard” tool on the basis of its potential to reduce or even eliminate bias. However, it is important to note that randomized controlled clinical trials typically include highly selected patients and investigators. Furthermore, monitoring and auditing in clinical trials results in higher quality of care in comparison with the usual medical care situation. Finally, informed consent, established as an ethical prerequisite around 1980, is associated with marked bias regarding study results [50]. Arguably, medical trials are based on a quasi-experimental design with hard end points that are far from everyday clinical routine. They have a strong potential for study bias and unclear relevance to clinical practice.

Many regulatory authorities, such as the Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMA), recommend placebo-controlled trials, and the scientific rationale behind placebo controls is well understood and widely accepted. However, ethical concerns arise regularly about the use of placebo controls in some settings. On the basis of their interpretation of the Declaration of Helsinki, Ken Rothman and Karen Michels asserted that placebo-controlled trials were always unethical unless there was no known effective treatment for the condition being studied [51]. This raised a number of concerns for trial design, and a clarification was issued in 2001 that stated that placebo-controlled studies were acceptable if scientifically necessary and if there was no risk of serious or irreversible harm to patients.

Therefore, apart from the efficacy level based on the results from randomized controlled trials, we also need to look at effectiveness and efficiency studies in order to determine the value of medical strategies. Industry and academia are challenged to cooperate on large phase III trials to determine whether randomized controlled trials can be translated into routine care. An example of a large phase III trial is the ProGORD study, a prospective, multicenter, open cohort study (industry-sponsored) designed to investigate endoscopic and symptomatic progression of gastroesophageal reflux disease under routine care, disease-related costs, quality of life, and risk factors for progression of gastroesophageal reflux disease and Barrett's esophagus [52]. To reduce or even avoid potential conflict of interest, the study organization includes an independent steering committee, an academic review board, an ethics committee and data protection approval, independent statistical analysis, and outside expert advice. It is through this combined approach, with ethical safeguards for industry and the clinician, that the best medical strategies will be developed, and ultimately individual patients will benefit from the knowledge gained.

All researchers, whether industry-funded or not, should have a common goal, as described by Sir William Osler: “To wrest from nature the secrets which have perplexed philosophers in all ages, to track to their sources the causes of disease, to correlate the vast stores of knowledge, that they are quickly available for the prevention and cure of diseases – these are our ambitions.”

Ethical challenges in drug phase I and phase II clinical trials

From the pharmaceutical industry's point of view, there are certain ethical challenges in drug phase I and phase II clinical trials which also have a bearing on phase III and phase IV trials [53].

Phase I trials. The transition from preclinical testing of a new compound to the first studies in man is in many ways the most important step in drug development. For a study to be ethically sound, the scientific and medical rationale must be right in order to document efficacy, safety, and tolerability.

The main ethical considerations must be:

- ▶ Is the area worth studying?
- ▶ Is the area researchable?
- ▶ Does the drug have the potential to become a medicine for patients?

It is also important to make sure that there is a strategic fit for the company, i.e. preclinical, clinical, and marketing competence in the company with regard to the therapy area in question. It is equally important that there is competence to correctly evaluate the data that are generated in the early phases, in particular regarding animal and human safety findings, in order to guarantee that no undue harm will come to patients. It is important that people in the company who are outside the project team are involved in the process of allowing a substance to be administered to man for the first time. Many companies have found that having a specific committee with competence and experience in drug development is of great value. Using people outside the company can also be valuable, even if the final responsibility always lies within the company. Discussion with ethics committees and/or health authorities can also be useful for tricky questions.

Starting phase I studies with a new compound always raises major concerns. The healthy subjects will not gain anything themselves for participating and this makes safety the main focus. It is also important to try to use healthy subjects who are as representative as possible of the intended patient population. The dosage of the substance and the use of placebo should be given special attention.

The level of financial compensation is important. It should be neither too high, nor too low. Local practice should be considered and it is of great importance that local laws are strictly adhered to.

The selection of clinics and centers should be based on the competence and experience of the participating centers, keeping the safety aspects and handling of medical emergencies always as a first priority. It is also important to have predefined go/no-go criteria for the correct evaluation of results in order to decide whether or not to proceed.

Phase II trials. Before entering into phase III, a thorough evaluation of risk–benefit must take place, also involving people not belonging to the project team. The ethical issues are different from those associated with phase I trials. In phase II trials we have to focus on issues such as choice of comparator, dosage, the use of placebo, the number of patients required, and clinical and statistical significance. The use of a safety monitoring board must be decided on, as well as potential interim analysis of safety and levels of compensation.

Biologicals

When dealing with biologicals the potential hazards of viruses and prions must be analyzed and the possibility of antibody formation must also be taken into account. The predictability of an-

imal toxicology findings for studies in humans needs special consideration.

A specific ethics issue is linked to substances that are used for testing a concept rather than for their potential to become a drug for a wide variety of patients. In this case there is a delicate balance between the advantage of advancing the knowledge about a concept and drug and the knowledge that it might be possible to find substances of the same type which with more favorable pharmacokinetic properties but which are still in much earlier phases of development.

Another ethical aspect here is that there is a general trend in drug development toward an increasingly risk-averse attitude, which could result in the failure to explore scientifically interesting options because of the potential risks, even where the benefits could be substantial.

The fine line between true innovation and selling points in medical endoscopy

Do higher expectations in business affect the style and the decision-making processes in the biomedical business environment? Certainly the decisive elements during the selection of selling points must concentrate on pragmatic aspects of how to balance the ethical dilemma of a true innovation focus and promoted selling points. The dynamism of today's business can not be excluded from biomedical enterprises. The pressure of delivering true innovation is immense. There is no doubt that a new feature of a biomedical product that is regarded as a true innovation is a clear selling point. The situation is changing because not every selling point is a true innovation. On analysis, the factors which influence the final marketing approach [54,55] can be categorized as:

- ▶ At the very beginning, a new feature has to be feasible with regard to technology, production capabilities, and safety, and must stay within the given budget for the final product.
- ▶ Within the biomedical business environment the medical relevance or evidence needs to be underlined in study cases or, preferably, proved in randomized controlled trials.
- ▶ To become successful, a crucial point of a new product is the inventive ingenuity, which ensures fast adaptation and results in speedy and successful market penetration.
- ▶ Both the compliance with the enterprise's strategic direction and the expected business impact need to be considered – the better the product idea fits into the available framework, the faster the return on investment can be expected.
- ▶ A thorough assessment of the product's competitiveness indicates areas of focus for positioning, pricing, and final selling points.
- ▶ Ethical implications are gaining an increasingly important role. Pushing a product onto the market at an early stage, without satisfactory evidence for the commercial selling points can be disastrous. Failure to live up to the medical claims or, worse, adverse outcomes can be ruinous.

Internal processes therefore need to be well established in order to evaluate all these aspects. The accomplishment of this process needs time, but this is where pressure arises, because the time-span between the initial product idea and its final commercial availability – the time to market – is critical. The company's response to the question, "Can a biomedical company nowadays stick to and rely on true innovations only?" reflects the fundamental paradigm in handling business-related ethical aspects. Various factors influence the pros and cons of any individual project. There are no global answers because too many factors

influence any particular setup. Factors with a negative influence on the whole process include the presence of current or upcoming competitors, which increases time pressures, and health-care budget constraints, which do not allow a different, possibly more costly approach to be taken. On the other hand, factors which can have a positive impact include generous investment in continuous basic research, a broad product portfolio (making dependence on the success of any one new product less threatening), the internal cultural environment, the long-term business strategy, and, finally, the need for compliance with newly established regulations and guidelines. Therefore, the positioning of a new product, whether true innovations are turned into selling points or whether selling points are simply "made up", is a crucial issue in today's biomedical market environment. It is a difficult decision-making process – sometimes only time will tell. However, a positive ethical climate within an organization should bring up issues that need to be addressed in order to find the right balance. The senior management focus nevertheless is an important key factor to ensure the appropriate framework.

As far as the use of devices that are eventually used on human subjects is concerned, it has been reported that in some cases these have been used in spite of failure to observe the fundamental principle that all devices must be designed and manufactured in such a way as to remove or minimize as far as possible the risk of physical injury. In a collaborative study with industry concerning medical devices and their use in patients, it is of paramount importance to realize that the purpose of the study is to determine whether a device is safe and effective, and not merely to test its safety.

Conclusions

The number of industry-sponsored trials has increased greatly in recent years. However, the motives and integrity in the reporting of some of their results have been questioned, while some authors have gone as far as to alarm the medical community by reporting that these trials could potentially better serve the interests of industry than the interests of patients. Surveys have shown that manipulation of clinical trials – by their design, analysis, or interpretation – is possible. Even when the results for an active therapy and control therapies are the same, industry-sponsored trials have been shown to reach a positive conclusion in favor of the sponsor's product five times more often than is the case in not-for-profit-sponsored trials.

However, we should not jump to the conclusion that industry is responsible for every ethical discrepancy. After all, it is primarily physicians who conduct the research, government bodies and institutions agree with their conduct when their regulations are observed, and journals publish their results provided their laid-down guidelines are recognized. Indeed, individuals coming from different starting points and with diverse educational and social backgrounds collaborate with the medical investigators in any given research trial, sharing with them the same interests, the same motives, and, most importantly, the same ethical principles. The prime goal of every single contributor is to serve the needs of those who seek medical care and attention.

Consensus statements accepted by voting

- ▶ From an ethical point of view, the introduction of a new pharmacological agent must fulfil expectations at all levels of performance, i.e. in terms of efficacy, effectiveness, efficiency.

- ▶ Trials initiated by the industry or institutions should be carried out using the same standards.
- ▶ Clinical trials should demonstrate the following features: the existence of an underlying medical/scientific rationale; correct design; focus on safety; competence with regard to both company and investigators; adequate technology; and external and internal guidance.
- ▶ A positive ethical assessment should become a routine part of the selling stage of endoscopic innovations.
- ▶ In any collaborative study with industry concerning medical devices and their use in patients, it is of paramount importance to realize that the purpose of the study is to determine whether a device is safe and effective.

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